SURGERY

VOL. 11 MAY, 1942 No. 5

Original Communications

THE LOCAL IMPLANTATION OF SULFANILAMIDE IN THE PERITONEAL CAVITY AND ITS CLINICAL APPLICATION IN PERITONITIS

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FEW eras in the history of man have been as productive of far-reaching radical changes in the way of life as the present. We have seen pre-eminently two startling developments, which, as medical men and as human beings, have impressed us because of the very oppositeness of their implications. One is the development of sulfanilamide with its unheralded powers of salvation in man's fight against suffering and death, and the other is the revolution of established military concepts and the perfection of new technique in the art of killing men—war.

Despite the constant refinement of surgical technique, numerous ingenious devices, mechanical and medical, to decompress the patient, improvement of pre- and postoperative care, the cryptic admission must still be made—too many patients die of peritonitis. The mortality of peritonitis from appendicitis alone is appalling, viewed from the standpoint of surgeon, statistician, or layman. Perhaps the most significant work to appear in recent years on the treatment of peritonitis associated with appendicitis is that of Ravdin, Rhoads, and Lockwood.[1] In a series of 809 consecutive cases of acute appendicitis, they were able to reduce the mortality from 1.5 per cent in the first 552 cases to 0.4 per cent in the last 257 cases. They attributed this marked improvement to the employment of sulfanilamide, orally and parenterally, in all severe cases of the latter group, no other factor being changed.

Originally deemed a specific for infections due to the beta-hemolytic streptococcus the impression was not easily shaken, and the earlier use of prontosil and its derivatives was quite restricted. It is very interesting to note, however, that the first recorded clinical report on the use of prontosil appeared in 1933, a case of staphylococcus septicemia successfully treated in a child 10 months of age.[2] Thus the history of

Received for publication, June 30, 1941.

the prontosil as well as its allied chemotherapeutic derivatives is one of apparent contradictions. We have seen how sulfanilamide, originally labeled for beta-hemolytic streptococcus, has successfully combated many infections, among others those due to gonococcus, pneumococcus, brucella, colon bacillus and Ducrey's bacillus.

Although the mode of action of sulfanilamide is not yet clearly understood, it has been hitherto shown that to be effective sulfanilamide must gain contact with the invading organism, and this is usually by means of the circulating blood. Colebrook and his co-workers and Long and Bliss have shown that sulfanilamide possesses bacteriostatic properties in dilutions as great as 1:10,000 and higher.[3] Yet no tissue damage had been demonstrated in parenteral and intrathecal injections in solutions of 1 per cent. These foregoing facts and also consideration of sulfanilamide's apparent disregard for specific labels led us independently early in 1939 to implant sulfanilamide powder, later crystals, in all traumatic wounds that were infected or that had potentiality of infection—cuts, lacerations, abrasions. We reasoned, perhaps naïvely, that if this peculiar drug's effectiveness at a given site depended upon being circuitously carried there by the blood after absorption via the gastrointestinal tract, why could not we, under favorable conditions, put it there in the first place? Thus empirically used, the results were highly gratifying; we saw no evidence of tissue irritation; most infected wounds healed quickly, and potentially infected cuts healed per primam after suture. These results were certainly contrary to what should be expected in the light of the current opinion based on studies in vitro. Long and Bliss[3] and others denied the possible efficacy of sulfanilamide applied locally.

In July, 1939, appeared the highly significant work of Jensen, Johnsrud, and Nelson on the direct implantation of sulfanilamide into compound fracture wounds.[4] Thirty-nine cases were presented, including 2 compound dislocations, all contaminated, all débrided, all closed and healed per primam. Our next anticipated venture was the implantation of sulfanilamide directly into the peritoneal cavity in peritonitis, and opportunity came on Dec. 16, 1939, in the form of a ruptured pelvic appendix with peritonitis, the case report of which is later presented (Case 1).

In this report we present our experiences with sulfanilamide implanted directly into the abdomen in cases of peritonitis and appendical abscesses as encountered in a private practice. Also is included a clinical study of sulfanilamide blood levels in these patients following intraperitoneal implantation, and collateral experimental studies using the rabbit. The laboratory animals were used to compare the drug's blood concentration with intra-abdominal concentration at time intervals, and to examine the peritoneal tissues microscopically for possible pathologic changes.

ILLUSTRATIVE CLINICAL CASES

CASE 1.—M. T., a boy, 15 years of age, entered the hospital Dec. 16, 1939, with history of stomach-ache of three days' duration. On the day previous to entry, he had taken castor oil and a painful bowel movement followed. At 3:30 P.M. on the day of entry, he suffered a sudden severe lower abdominal pain, followed by nausea and vomiting, after which the pain remained constant and severe, and his "stomach stayed hard." Physical examination revealed a well-developed boy with temperature, 100°; pulse, 118; respiration, 20; blood pressure, 118/60. Examination of heart and lungs was negative. The abdomen was held rigid with maximum tenderness in the suprapubic region; rebound tenderness was present. Rectal examination showed definite tenderness to the right. A diagnosis of ruptured pelvic appendicitis was made.

Appendectomy was performed under spinal anesthesia about three and one-half hours after approximate time of rupture. A perforated pelvic appendix was found with pelvic pus accumulation. The appendix was removed and the pelvic peritoneal cavity lavaged with about 500 c.c. of normal saline solution. One gram of sulfanilamide crystals was placed in the appendix bed, and the abdomen closed, using 0.5 Gm. sulfanilamide in the wound. A small Penrose drain was inserted. The temperature dropped to normal on the second postoperative day. Recovery was uneventful and the patient walked from the hospital on the ninth postoperative day.

This was the first case in which we used sulfanilamide crystals intraperitoneally, hence the trial dose was one gram, and a drain was placed. Nevertheless, in the light of previous tedious experiences with similar cases of pelvic peritonitis, we were quite elated with the results, and the incentive to enlarge our experience was stimulated.

CASE 4.—A. I., male, 20 years of age, entered the hospital April 13, 1940, with history of stomach-ache since that morning, five hours later a lower abdominal pain with a desire to defecate, then a sudden severe pain in the lower midabdomen followed by nausea and vomiting. Physical examination revealed temperature, 104°; pulse, 118; respiration, 20; blood pressure 115/50. Examination of the heart and lungs was negative. The abdomen was tender in the right lower quadrant and suprapubic region with definite rebound tenderness. Urinalysis showed occasional pus cell and occasional *B. coli*. A diagnosis of ruptured pelvic appendicitis was made.

Appendectomy was performed under spinal anesthesia, and a perforated appendix was found in the pelvis. The pelvic peritoneal cavity was lavaged with warm normal saline solution, and 8 Gm. of sulfanilamide were placed in the pelvis. One gram was distributed in the wound and the abdomen closed without drains. Pus culture from the appendix was reported *B. coli*. The temperature was normal on the first postoperative day, but began to rise on the second. Sulfanilamide was given orally, gr. 10 with sodium bicarbonate t.i.d. The temperature again dropped to normal after one day, but oral sulfanilamide was continued for three days. The patient made an uneventful recovery and left the hospital ambulatory on the seventh postoperative day.

CASE 11.—Y. N., a man, 63 years of age, entered the hospital on July 27, 1940, via ambulance after excruciating upper abdominal pain of sudden onset four hours previous to entry. (A diagnosis of carcinoma of stomach with partial obstruction had been made the previous week; refusing operation, the patient had been discharged just five days before.) Physical examination revealed a patient resting quietly under the influence of adequate opiates. Temperature, 98.4°; pulse, 60;

respiration, 20; blood pressure, 95/65. The heart and lungs were negative. The abdomen showed marked rigidity, general tenderness to pressure, marked rebound tenderness, obliteration of liver dullness to percussion. Urinalysis negative for sugar and albumin, microscopically a few fine granular casts present. R.B.C., 4,480,000; Hgb., 96 per cent Sahli; W.B.C., 6,000; polymorphonuclears, 86 per cent. Diagnosis: Carcinoma of the stomach ruptured, with peritonitis.

Operation was performed under high spinal anesthesia five hours after rupture. On opening the peritoneal cavity through an upper middle incision, escapage of gas was noted, peritoneal surfaces inflamed, abdomen soiled by partially digested rice and vegetables with high odor of vomitus. Perforation of about 1 cm. was found on anterior wall at lesser curvature just proximal to pyloric ring, food particles, bubbles, and liquid matter still issuing. The tumor mass around the perforation was about the size of a small egg, hard, firmly adherent, and infiltrating pancreatic tissue. Lesser sac was also filled with stomach content. Subtotal gastric resection and antecolic gastroenterostomy performed, mobilization of the pyloric end required adequate removal of involved pancreatic tissue. One bean-sized indurated subpyloric gland was removed, with no further evidence of metastasis. Peritoneal cavity was thoroughly lavaged clean of an immense amount of debris. Eight grams of sulfanilamide were implanted circa anastomosis and center of soilage, two grams in wound layers. The abdomen was closed without drainage. Seven grams sulfanilamide were given by hypodermoclysis on the first two postoperative days. Daily blood and urine examinations showed no significant changes. Although this patient had a febrile postoperative course, due chiefly to bronchopneumonia, there were no intra-abdominal complications. On the eighth postoperative day, during a cough seizure, the lower two inches of the wound gave way and he eviscerated about three feet of small intestine. The bowel loops were washed with normal saline solution, coated with 4 Gm. of sulfanilamide, returned to the abdomen, and the wound repaired. There were still no abdominal complications, no wound infection.

CASE 12.—M. F., male, aged 21, taken to hospital August 17, 1940, with severe lower abdominal pain since early morning, unrelieved by morphine. History of midabdominal pain five days before gradually increasing in severity with localization below navel day before entry. Had three watery bowel movements on the same day with no urinary symptoms. Physical examination revealed a patient, quite toxic, moaning and restless with pain, thighs flexed on abdomen. Temperature, 98.6°; pulse, 68; blood pressure, 120/70. Examination of heart and lungs was negative. Abdomen flat, showing generalized rigidity and tenderness, maximal tenderness and rigidity in lower right quadrant. No audible peristalsis. Urine negative for albumin, sugar, and sediment. Hgb., 110 per cent Sahli; W.B.C., 24,400 with 88 per cent polymorphonuclears. Diagnosis: ruptured appendix.

Operation was performed under spinal anesthesia; purulent fluid noted immediately on opening the peritoneum. Exactly 100 c.c. thick, purulent material aspirated from the pelvis. A large appendix covered with plastic exudate, containing two large fecal stones, and bearing two perforations was removed from a low retrocecal position. The pelvic cavity and appendix "bed" were thoroughly lavaged with warm normal saline solution. Ten grams sulfanilamide crystals were distributed in the pelvis and the appendix bed, and the closure was without drainage, using one gram sulfanilamide in the wound layers. From the second to sixth postoperative day, sulfanilamide was given orally, 10 gr. t.i.d. with soda bicarbonate. Temperature reached normal on the fourth postoperative day and rose to 99.2° on the fifth, due to wound hematoma. The patient was discharged ambulatory on the seventh day.

The sulfanilamide we employed was stocked in glass ampoules in crystalline form by the Abbott Laboratories. Beyond receiving assur-

ance of its sterility by private communication with the manufacturers no further bacteriologic studies were made. The crystals were transferred to a sterile dry cup and poured directly into the abdominal cavity.

In recapitulation, given an adequately prepared patient, our operative technique is essentially as follows:

1. Spinal anesthesia is the anesthesia of choice; ether or local novocain is used as indication demands.

2. The abdomen is opened through any incision appropriate to the condition, but the McBurney is the incision of choice in our appendectomies.

3. The field is isolated with moist gauze packs, and the abdominal wound protected with towels. Lately we have been using waterproof cellophane incorporated between gauze layers for wound protection, and we believe wound infections have been further decreased.

4. Thorough aspiration of pus and infective material from the abdomen is stressed; all possible gangrenous tissue is removed; and further, the regional abdomen is cleansed by repeated perfusion with warm normal saline solution and suction.

5. Crystalline sulfanilamide in amounts of 4 to 10 Gm., depending on the patient's age, is implanted directly in the area of greatest infection, with 2 to 3 Gm., governed by the size of the incision, used to coat wound layers and surfaces before closure.

6. Pus per se is no indication for drainage. Drains are limited to instances in which irremovable gangrenous tissue or tissue of doubtful viability must be left behind at closure.

7. Supplemental sulfanilamide therapy is continued orally after the first postoperative day. After surgical procedures involving anastomosis of hollow viscera, and in patients unable to take oral medication, the sulfanilamide is given parenterally.

EXPERIMENTAL FINDINGS

In December, 1939, we arbitrarily placed one gram of sulfanilamide into the pelvic peritoneal cavity of a patient with peritonitis from a ruptured pelvic appendix. Jensen and co-workers[4] had shown that 5 to 15 Gm. could be safely implanted in compound fracture wounds and closed. In the succeeding three cases we, therefore, felt safe in employing doses of 8 to 10 Gm. The results were encouraging, but the dosage was still quite arbitrary. At this point, to establish some rational basis for further work, we enlisted the technical assistance of our coauthor, Dr. O. B. Pratt, and the facilities of the White Memorial Hospital Laboratory.

METHOD

In the present investigation, white rabbits weighing an average of four pounds were used. Under ether anesthesia, the peritoneal cavity was opened and sulfanilamide crystals implanted, ranging in amounts

from 1 to 15 Gm. In four rabbits one gram was used (Fig. 1). Blood was taken from the heart at hourly intervals and the concentration of sulfanilamide determined. Microscopic sections were made of the intestines and the peritoneum at intervals to search for any possible pathologic changes.

In another series of ten rabbits, one gram of sulfanilamide was placed intraperitoneally and the rabbits sacrificed at hourly intervals (Fig. 2).

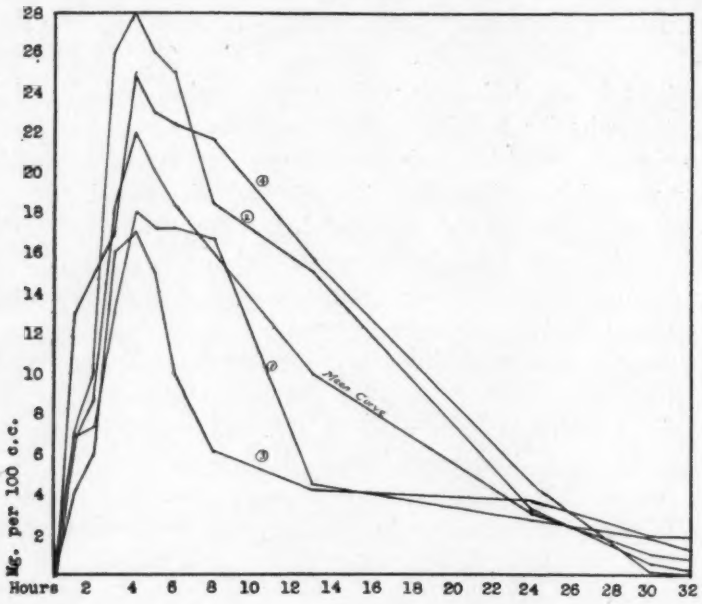

Fig. 1.—Hourly blood sulfanilamide levels in rabbits receiving 1 gram of crystalline sulfanilamide intraperitoneally.

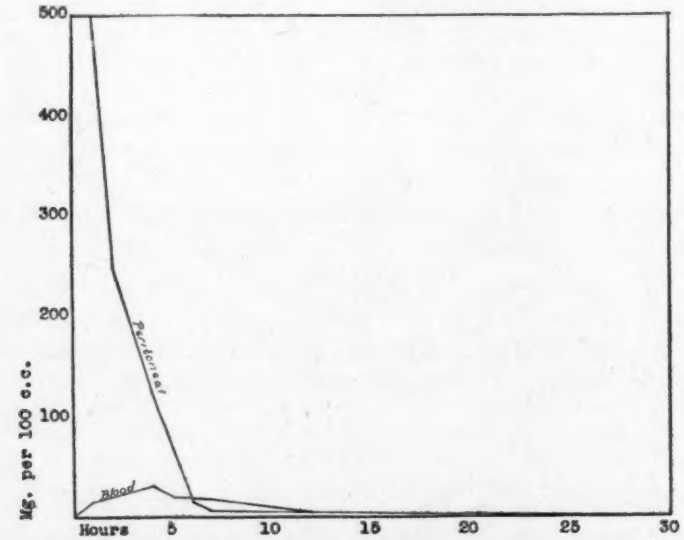

Fig. 2.—Comparison of intraperitoneal and blood concentration levels of sulfanilamide hourly in rabbits after intraperitoneal implantation of 1 gram.

The blood concentration was determined in each case and compared with the coincident intraperitoneal concentration; this local concentration was determined by rinsing the peritoneal cavity with 150 c.c. of sterile water to recover the dissolved sulfanilamide.

The other portion of our investigation dealt with the determination of blood sulfanilamide levels in patients after known quantities of sulfanilamide were implanted intraperitoneally and the abdomen closed without drainage.

RESULTS

Fig. 1 shows that the average maximum concentration in the blood was 22 mg. per 100 c.c. in rabbits that received one gram intraperitoneally.

Rabbits that received 2 Gm. of sulfanilamide had a maximum blood concentration of 57 mg. per 100 c.c. but died in thirty-six hours. Rabbits that received 15 Gm. had a maximum blood concentration of 270 mg. per 100 c.c. and died in fifteen hours.

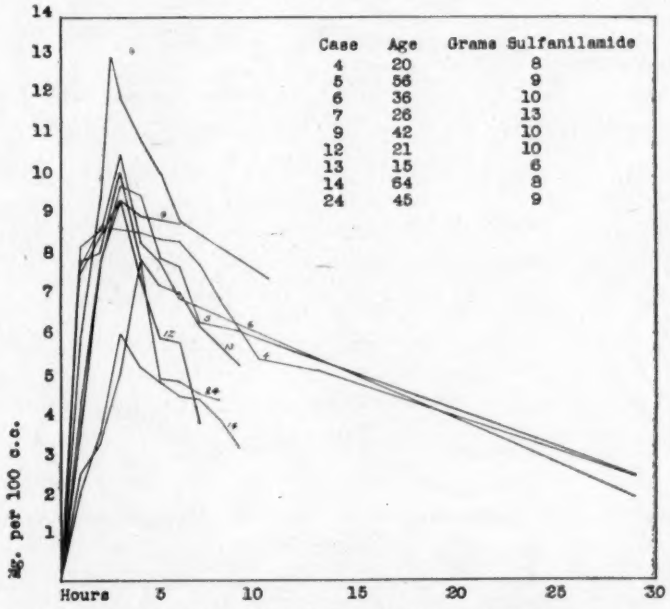

Fig. 3.—Hourly blood sulfanilamide levels in patients receiving known quantities of sulfanilamide intraperitoneally at operation.

Fig. 2. It is seen that there was a rapid fall in the intraperitoneal concentration as the blood concentration increased. At about six hours the sulfanilamide concentration in the blood about equaled the concentration in the peritoneal cavity, after which the blood concentration exceeded the peritoneal concentration.

Fig. 3. Concentration curves were plotted for patients receiving known amounts of sulfanilamide intraperitoneally at operation. In Case 4, nine grams were used and the blood concentration rose to 9 mg.; Case 5, nine grams showed a rise to 9.8 mg.; Case 6, ten grams showed

TABLE I

SHOWING HOURLY BLOOD SULFANILAMIDE CONCENTRATION IN RABBITS RECEIVING ONE GRAM OF SULFANILAMIDE INTRAPERITONEALLY

TIME (HOUR)	BLOOD SULFANILAMIDE CONCENTRATION MG./100 C.C.				
	RABBIT I	RABBIT II	RABBIT III	RABBIT IV	AVERAGE
1	6.8	7.0	4.0	13.0	7.7
2	7.3	10.0	6.0	15.0	9.5
3	12.9	26.0	16.0	17.0	18.0
4	18.0	28.0	17.0	24.8	22.0
5	17.2	26.0	15.0	23.0	20.3
6	17.2	25.0	10.0	22.5	18.7
7	17.0	22.0	8.0	22.0	17.2
8	16.8	18.5	6.0	21.8	15.7
9	14.5	17.8	5.8	20.5	15.4
10	12.0	17.0	5.4	19.2	13.4
13	4.5	15.0	4.2	16.0	10.0
18	3.8	9.6	4.0	10.5	6.9
24	2.8	3.2	3.8	4.5	3.7
30	2.6	0.5	2.0	0.3	1.3

10.8 mg.; Case 7, thirteen grams showed 13.1 mg.; Case 9, ten grams showed 9.4 mg.; Case 12, ten grams showed 9.4 mg.; Case 13, six grams showed 10.2 mg., Case 14, eight grams showed 6.1 mg., and Case 24, nine grams showed 7.9 mg.

The maximum blood concentration of sulfanilamide was reached almost uniformly in three hours in patients as compared to four hours in rabbits. In older individuals, the gradient is not as steep, perhaps due to natural cardiovascular and renal changes.

No significant pathologic changes, gross or microscopic, were seen in the intestines or peritoneum of rabbits following direct contact of these tissues with sulfanilamide crystals by intraperitoneal implantation.

DISCUSSION

No effort has been made to classify our peritonitis cases into the classically described local, spreading, and general forms, feeling with

TABLE II

COMPARING HOURLY INTRAPERITONEAL AND BLOOD CONCENTRATION OF SULFANILAMIDE IN RABBITS

TIME (HOUR)	BLOOD CONCENTRATION	INTRAPERITONEAL CONCENTRATION
	MG./100 C.C.	MG./100 C.C.
1	15.0	500
2	20.0	245
3	26.0	180
4	30.0	120
5	20.0	70
6	19.8	20
7	18.5	8
8	15.0	5
9	14.0	4
10	10.0	4
12	4.0	4
15	4.0	3
20	3.0	2
25	2.0	1
30	0.5	trace

others that little is to be gained. Fortunately, we see our cases early, but, in any event, operation is decided by the patient's immediate condition rather than by the relative area of peritonitis involved, or the time elapsed since its onset.

The bacteriology of appendical peritonitis has been shown to be far from specific; the various streptococci are found, anaerobes of the Welch type occur, but the colon group is to be considered the most common invader, and generally, our greatest foe. In ruptured peptic ulcers also streptococci and colon bacilli are chiefly the organisms found.[5]

In treating peritonitis with sulfanilamide given orally, Ravdin and co-workers[1] at first discontinued the drug in forty-eight to seventy-two hours in the earlier cases of their series when the culture failed to show hemolytic streptococci. Following the work of Helmholz,[6] who demonstrated the effectiveness of sulfanilamide against *Escherichia coli,* they then employed it in all cases when this organism was found, then, "before long it was employed in all cases regardless of culture report." Mellon and collaborators,[7] too, in commenting on the wholly unanticipated therapeutic properties of sulfanilamide given by the usual routes and the extensive nonspecificity of its action is reminded by its remarkable behavior of a "general internal disinfectant."

Perhaps some criticism may be forthcoming of one phase of the surgical technique employed, namely, the "lavage" of the infected peritoneal cavity. In the usual early case of ruptured appendix certainly no attempt is made to lavage the entire abdomen. When tenable, the field contaminated by free pus is walled off by gauze packs and the area washed clean by alternate perfusion with warm normal saline solution and suction. Gangrenous and devitalized tissue is removed when possible; the appendix is never left behind. Walled-off collections of pus and appendical abscesses are likewise washed out, with the usual respect as to formed natural barriers. On the other hand, when the whole peritoneal cavity has been contaminated by the sudden rupture of an ulcer, and infective material and gross food particles are strewn among the bowel loops, all accessible areas are washed out in turn.[8] The senior author for many years has followed this procedure in ruptured ulcers, and regional lavage in appendical peritonitis with uniformly satisfactory results.

In 1938 Lockwood[9] showed that peptones ("pus," as encountered) markedly interfered with the bactericidal action of sulfanilamide on the hemolytic streptococcus. Meleney and Harvey[10] noted that sulfanilamide given orally acted the most dramatically in early hemolytic streptococcus infections in which tissue necrosis and thrombosed blood vessels were not present to prevent contact of the circulating drug with the invading organism. In the presence of tissue necrosis or abscess formation in infections, efficacy of sulfanilamide has been found definitely limited, and debridement and surgical drainage must be done to effect healing.

TABLE III

CASE NO.	AGE	SEX	DIAGNOSIS	DURATION OF SYMPTOMS	PROCEDURE	SULFANILAMIDE	DRAIN	POSTOPERATIVE COURSE
1	15	M	Ruptured pelvic appendicitis	3 days	Appendectomy	1 Gm.	Yes	Afebrile on 2nd p.o. day. Discharged on 9th p.o. day. No complication.
2	54	M	Stab wound in small intestine	16½ hr.	Simple closure	8 Gm.	Yes	Afebrile on 2nd p.o. day. Uneventful p.o. course. Discharged 13th p.o. day.
3	40	M	Perforated gastric ulcer	18 hr.	Simple closure with gastroenterostomy	10 Gm.	No	Afebrile on 4th p.o. day. Uneventful p.o. course. Discharged 9th p.o. day.
4	20	M	Ruptured pelvic appendicitis	8½ hr.	Appendectomy	8 Gm.	No	Uneventful p.o. course. Discharged on 7th p.o. day.
5	56	M	Perforated appendicitis (50 c.c. pus in pelvis)	2 days	Appendectomy	9 Gm.	No	Uneventful p.o. course. Discharged on 7th p.o. day.
6	36	F	Perforated duodenal ulcer	6 hr.	Simple closure	10 Gm.	No	Uneventful p.o. course. Afebrile 4th p.o. day. Discharged 13th p.o. day.
7	26	M	Ruptured retrocecal appendicitis	24 hr.	Appendectomy	13 Gm.	No	Uneventful p.o. course. Afebrile 2nd p.o. day. Discharged 7th p.o. day.
8	48	M	Ruptured retrocecal appendicitis	39 hr.	Appendectomy	8 Gm.	No	Uneventful p.o. course. Discharged 7th p.o. day.
9	42	M	Perforated gastric ulcer	5 hr.	Simple closure	10 Gm.	No	Uneventful p.o. course. Discharged 9th p.o. day, ambulatory. Afebrile on 4th p.o. day.

10	37	F	Acute right salpingo-oophoritis (gonococcic) with peritonitis	3 days	Salpingo-oophorectomy right	8 Gm.	No	Uneventful p.o. course. Afebrile 9th p.o. day and discharged ambulatory on the same day.
11	63	M	Perforated gastric carcinoma	5 hr.	Subtotal gastrectomy	8 Gm.	No	Evisceration on 8th p.o. day. Exacerbation of pulmonary tuberculosis.
12	21	M	Ruptured retrocecal appendicitis (100 c.c. pus in pelvis)	5 days	Appendectomy	10 Gm.	No	Wound hematoma. Discharged on 7th p.o. day.
13	15	M	Ruptured pelvic appendicitis	5 hr.	Appendectomy	6 Gm.	No	Wound hematoma. Discharged ambulatory on 8th p.o. day.
14	64	M	Ruptured appendicitis	24 hr.	Appendectomy	8 Gm.	No	Wound infection. Discharged on 7th p.o. day.
15	19	F	Ruptured retrocecal appendicitis (30 c.c. pus aspirated)	4 days	Appendectomy	8 Gm.	No	Fecal fistula. Discharged from hospital on 22nd p.o. day with fecal fistula still draining.
16	5	M	Appendical abscess	7 days	Appendectomy	4 Gm.	Yes	Uneventful p.o. course. Afebrile on 4th p.o. day. Discharged 8th p.o. day.
17	10	M	Ruptured retrocecal appendicitis	6 days	Appendectomy	4 Gm.	No	Wound infection. Discharged on 13th p.o. day.
18	52	M	Appendical abscess	3 days	Appendectomy	8 Gm.	Yes	Uneventful p.o. course. Afebrile on 4th p.o. day. Discharged on 8th p.o. day.
19	57	M	Perforated laterocecal appendicitis (gangrenous)	24 hr.	Appendectomy	8 Gm.	Yes	Wound infection. Discharged on 9th p.o. day.
20	16	F	Ruptured subcecal appendicitis	16 hr.	Appendectomy	3.5 Gm.	No	Wound hematoma. Discharged on 7th p.o. day.

TABLE III—CONT'D

CASE NO.	AGE	SEX	DIAGNOSIS	DURATION OF SYMPTOMS	PROCEDURE	SULFANILAMIDE	DRAIN	POSTOPERATIVE COURSE
21	5	M	Appendical abscess	3 days	Appendectomy	4 Gm.	Yes	Wound infection. Discharged on 9th p.o. day.
22	45	M	Ruptured retrocecal appendicitis	37 hr.	Appendectomy	9 Gm.	No	Uneventful p.o. course.
23	13	F	Ruptured pelvic appendicitis	2¼ days	Appendectomy	7 Gm.	No	Wound infection. Discharged on 9th p.o. day.
24	25	M	Appendical abscess	12 days	Drainage only	8 Gm.	Yes	Afebrile on 6th p.o. day. Discharged on 9th p.o. day.
25	13	F	Ruptured retrocecal appendicitis	6 days	Appendectomy	4 Gm.	Yes	Afebrile on 3rd p.o. day. Discharged on 7th p.o. day.
26	7	M	Ruptured pelvic appendicitis	11 hr.	Appendectomy	4 Gm.	No	Partial bowel obstruction on 7th p.o. day.
27	12	F	Pneumococcic peritonitis (50 c.c. pus aspirated)	1 day	Appendectomy	6 Gm.	No	Afebrile on 2nd p.o. day. Discharged on 8th p.o. day.
28	33	M	Ruptured appendicitis (60 c.c. pus aspirated)	12 hr.	Appendectomy	8 Gm.	No	Afebrile on 4th p.o. day. Discharged on 8th p.o. day.
29	27	M	Ruptured subcecal appendicitis	33 hr.	Appendectomy	4 Gm.	No	Afebrile 3rd p.o. day. Discharged 7th p.o. day.
30	62	M	Gangrenous cholecystitis and general peritonitis (65 c.c. exudate aspirated)	4 days	Cholecystostomy without peritoneal drainage	8 Gm.	Yes	No wound infection. Afebrile 2nd p.o. day. Discharged 14th p.o. day.

Since starting to employ sulfanilamide intraperitoneally, we feel more than ever that lavage of the infected area is indicated to mechanically remove as much as possible the pus which serves as a deterrent to the action of sulfanilamide. All surgeons have been astounded at the amount of foul pus that can be aspirated from the pelvic cavity in cases of ruptured pelvic appendicitis (50 to 320 c.c. in our cases by actual measurement). We have seen the necrotic and "cooked" appearance of appendical "beds" when a gangrenous retrocecal appendix has ruptured and almost disintegrated in a pool of pus. We have closed with dams and drains and later spent many days changing the foul-smelling dressings, the veritable "pus compresses" which were sure to follow—anxious, miserable, expensive days for the patient, with always the threat of intestinal obstruction under an unsightly scar. This side of the picture is rarely presented, or glossed over, when surgical reports are written; it is taken for granted. Since sulfanilamide has been added to our armamentarium we have been able to close most of these cases confidently without drains, secure primary wound healing, and discharge these patients promptly after smooth postoperative courses.

Regardless of the amount of pus in the abdomen, we limit drainage to only those cases with extensive irremovable devitalization of tissue. Lockwood and Ravdin[11] in tabulating the improvement in appendicitis mortality since using sulfanilamide (parenterally and orally) show only one death in 318 cases, truly an admirable record. Still, 41 per cent of these cases were drained. It is our belief that the number of cases requiring drainage could be rendered exceedingly small by the local use of sulfanilamide, after adequate removal of pus by suction and judicious lavage of the infected area with normal saline solution. We feel that the so-called danger of "spreading the infection" has been highly overestimated, that in most cases the infection is at least microscopically well beyond the area actually touched by the saline lavage.

The experiments with rabbits revealed that even lethal doses of sulfanilamide crystals placed directly in the abdominal cavity showed neither gross nor microscopic evidence of tissue damage. The study of the blood concentration of sulfanilamide in our patients after intraperitoneal administration of the drug showed that absorption was quite rapid, reaching the maximum in three hours, and that for each gram of intraperitoneal sulfanilamide we could expect 1 mg. per cent concentration in the blood. In an experiment on dogs Ravdin and coworkers[1] demonstrated that one and one-half hours after administration of sulfanilamide by hypodermoclysis the peritoneal concentration was still less than one-half the blood level (41.6 to 43 per cent of blood level). Time being a precious element, especially in spreading peritonitis, we believe that the local use presents distinct advantages. Since the usual systemic medication aims to attain a blood level of 7 to 15

mg. per cent, we have at hand a precise method of attaining the desired therapeutic blood level in peritonitis within three hours. Thus, recently we have routinely employed 8 to 10 Gm. on the basis of the above findings. As pointed out by Jensen and co-workers,[4] reasoning from the solubility of sulfanilamide at body temperature (0.8 per cent), we have achieved within a few minutes at the very site of infection a concentration nearing 800 mg. per cent. A concentration adequately bactericidal for some organisms and bacteriostatic for others is maintained safely beyond the time at which the usually desired therapeutic blood level has been reached.

As shown by Fig. 3, our patients have a sulfanilamide concentration in the blood of from 5 to 8 mg. per cent at the end of 12 hours following operation, and at the end of twenty-four hours, it is still between 3 and 5 mg. per cent. Because of the massive single dosage with its rapid absorption we were concerned whether any consistent deleterious effect might be produced on the normal leucocyte reaction. In several cases closely followed we found no depression of the leucocyte count, the degree of leucocytosis being generally compatible with the severity of the infection and the response of the host. Thus in patient S.K., the preoperative leucocyte count was 13,600 with 86 per cent polymorphonuclears, the second postoperative day 11,900 with 85 per cent polymorphonuclears. In patient K.S., the preoperative count was 19,100 with 92 per cent polymorphonuclears; first postoperative day 15,600 and 78 per cent polymorphonuclears; second postoperative day 9,300 with 77 per cent polymorphonuclears; fourth postoperative day 6,800 and 81 per cent polymorphonuclears. On patient Y. N., a perforated gastric carcinoma case, daily blood counts were done for eleven consecutive days. The preoperative count was 6,000 with 86 per cent polymorphonuclears; it was 7,400 with 91 per cent polymorphonuclears on the third postoperative day, and on the eleventh day, the count was 8,200. In patient M.F., the preoperative leucocyte count was 24,400 with 88 per cent polymorphonuclears; on the third postoperative day, the count was 21,400 with 90 per cent polymorphonuclears.

In our limited series of cases we have encountered no untoward toxic manifestations. The patients are remarkably serene and comfortable on the first postoperative day and are generally able to continue sulfanilamide medication and take fluids orally. The drug is given parenterally after surgery involving the stomach or bowels, or if nausea precludes oral administration. We have also discovered that in our female patients we have not recently encountered the hithertofore occasional postoperative pyelitis and bladder infection. In passing, it may not be amiss to mention that in our service we feel we have almost overcome the surgeon's bugbear of wound abscesses by use of sulfanilamide prophylactically in operative wounds with potentiality of infection. It is likewise used intra-abdominally after gastric resec-

tion, enterocolostomy, gall-bladder operations, etc. We feel a sense of security after closure likened to that after Moynihan's "hypnotic stitch."

At the time this work was in early progress there was no medical literature extant describing the clinical use of sulfanilamide crystals in the peritoneal cavity. We found ourselves in the paradoxical position of trying to justify our successful cases. The literature on the sulfonamides is growing voluminous and it is gratifying to see that clinical as well as experimental reports appear to justify and indicate its intraperitoneal use.

Dees[12] reported a consecutive series of 25 cases of perforated appendices operated upon between November, 1939, and September, 1940. Only one patient was lost, operation being performed after an elapsed time of seven days, with the patient in a state of generalized peritonitis with abdominal distention. This author has used what seems to us an inordinately large amount of the drug, "A standard dose of sulfanilamide was used on all these cases: 20 grams," especially when his age group varied from four to sixty-eight years. No untoward drug reactions were recorded, and the author makes the interesting observation that "the greater the degree of peritonitis, the higher the blood concentration."

Key and Frankel[13] have further shown that in experimental animals sulfanilamide, sulfapyridine, and sulfamethylthiazole in powder form are well tolerated by the joints, muscles, and connective tissues. The drugs in solution were found well tolerated by joint, pleural, and peritoneal surfaces.

Recently Lockwood[14] has advanced a reasonable working hypothesis of the mode of action of sulfonamide drugs. These compounds bear a structural similarity to p-aminobenzoic acid, which is essential to bacterial nutrition. By virtue of this structural similarity the molecules of sulfanilamide are capable of competitively replacing molecules of p-aminobenzoic acid in the cycle of bacterial nutrition. The bacterial cells cease to divide and the resultant inhibition of bacterial reproduction may be called "bacteriostasis." Lockwood points out that "The concentration of sulfonamide required for complete bacteriostasis may be greater than is supplied the area through the physiologic process of drug transport. However, if the molecules of sulfonamide greatly outnumber the molecules of p-aminobenzoic acid, the bacteria cease to multiply, their toxin production stops, and they will die either from 'starvation' or by falling prey to the phagocytic cells of the host. When this sequence takes place in the body, the infection no longer spreads into new areas, the bacteria are destroyed, and the patient recovers."

P-aminobenzoic acid and the like substances present in pus and necrotic tissues, thus, in function, are sulfonamide inhibitors. It follows naturally that adequate removal of pus is of prime importance in treating purulent infections with sulfonamides, and peritonitis, we contend, should not be an exception.

Impressed by the groundwork of Lockwood, Rosenburg and Wall[15] proceeded to experiment with peritonitis in rats. The peritonitis was produced by injecting pus from clinical cases of appendicitis and peritonitis. In a series of 42 white rats, 20 of a possible 21 unprotected rats died of peritonitis. However, 11 out of 21 rats protected by the simultaneous injection of a sulfanilamide suspension lived indefinitely. In another experiment, 48 rats were given sulfanilamide either intraperitoneally or subcutaneously, four to twenty hours after production of peritonitis. With intraperitoneal treatment 17 good results out of 24 were reported, as compared with the 7 good results out of a possible 24 when sulfanilamide was given subcutaneously. From the experiments, although admittedly not conclusive, the authors felt some degree of protection was afforded by intraperitoneal implantation, more so than by the subcutaneous route. They recommend intraperitoneal implantation of sulfanilamide in peritonitis cases augmented immediately by subcutaneous sulfanilamide. Four clinical cases of peritonitis were presented with recovery in all: two cases of appendical peritonitis, a case of gross peritoneal contamination from bowel punctures during operation for intestinal obstruction, and a case of appendical abscess with bowel obstruction and contamination.

Thompson, Brabson, and Walker[16] reported on the intraabdominal use of sulfanilamide in acute appendicitis at the Roosevelt Hospital during the year 1940. It was employed in a total of fifty-nine, or 29 per cent of 204 cases, chiefly in those with peritonitis or abscess formation. Not a single patient was lost during the year—a mortality rate of zero! This was compared with a series of 741 similar cases at the same hospital operated upon during the period 1935 to 1939, including simple acute, peritonitis and abscess cases. There were twenty deaths, or a mortality rate of 2.7 per cent. With employment of sulfanilamide complications seemed less frequent and less severe, no local tissue destruction was found, and no severe toxic effects were encountered. The authors point out that a mortality rate approximating zero must not be expected with sulfanilamide since dissociated conditions, such as embolism, cannot be obviated. They are firmly convinced, however, that the dramatic reduction in their mortality rate is directly attributable to sulfanilamide.

Graham[17] of Brooklyn now employs intraperitoneal and subcutaneous sulfanilamide in appendicitis with peritonitis, gastric and intestinal resections, closure of colostomies, operations for intestinal obstruction, and perforations of hollow abdominal viscera, "with greatly improved results." This author employs 4 Gm. of sulfanilamide in 500 c.c. saline solution as the initial intraperitoneal dose.

Griswold and Antoncic[18] have analyzed 111 consecutive cases of perforated peptic ulcer seen from 1931 to 1940 at the Louisville City Hospital. They stress the importance of the streptococcus in relation to mortality and advocate the local implantation of sulfanilamide.

They recorded nine fatalities in thirty-one cases having positive cultures. Eight of the fatalities were associated with streptococcus. Among other things, their present technique includes suction removal of intraperitoneal and intrapelvic fluid, 5 to 10 Gm. sulfanilamide crystals sprinkled about the lesion with 3 to 5 Gm. in the abdominal wall, and the wound closure with silk using no intraperitoneal drains.

TABLE IV

SUMMARY OF RESULTS

NATURE	NO. OF CASES	REMARKS
Ruptured appendicitis with peritonitis	18	
A. Primary closure of the wound without drain	15	
1. Primary healing of the wound	7	
2. Wound hematoma	3	
3. Wound infection	4	
4. Intraperitoneal infection—fecal fistula	1	
B. Closure of the wound with drain	3	
Appendical abscess with drain	4	
Perforated peptic ulcer (primary closure of wound without drain)	3	Wound healed per primam
Perforated gastric carcinoma (subtotal gastrectomy) with primary closure of wound without drain	1	Evisceration on eighth p. o. day. Wound healed per primam
Stab wound in the small intestine (closure of wound with drain)	1	
Acute salpingitis with pelvic peritonitis (without drain)	1	Wound healed per primam
Pneumococcic peritonitis	1	Wound healed per primam
Gangrenous cholecystitis with generalized peritonitis	1	Wound healed per primam

Jackson[19] of Ann Arbor recently reported on the intraperitoneal use of sulfanilamide. He recognized it as a sound procedure. In his studies of blood sulfanilamide concentration after intraperitoneal implantation of therapeutic amounts in patients and dogs he found the peak level at about two hours, falling rapidly to almost nothing at the end of twenty-four hours. Twenty-five patients received sulfanilamide intraperitoneally at the University of Michigan Hospital during the year, 1940-41, indications being peritonitis, large bowel surgery, and peritoneal soiling with contents of the gastrointestinal tract. No fatalities were recorded in the peritonitis cases except in those in which sulfanilamide was not continued. The only complication which caused concern was icterus in six patients which was felt due to liver damage. The jaundice cleared on discontinuing the drug. Checking in experimental animals it was found that during the absorptive phase sulfanilamide levels after intraperitoneal implantation were 30 to 40 per cent higher in the portal blood than in the jugular vein.

SUMMARY AND CONCLUSION

1. A consecutive series of peritonitis cases have been presented in which sulfanilamide crystals were implanted intraperitoneally and the abdomen generally closed without drainage. There were no untoward reactions, no intra-abdominal complications, wounds healed per primam, and the patients were discharged promptly after generally smooth postoperative courses.

2. Collateral studies done on rabbits revealed that intraperitoneal absorption of sulfanilamide was very rapid, maximum absorption being in four hours; however, an extremely high concentration was maintained intraperitoneally until the maximum blood concentration was reached. No pathologic changes, gross or microscopic, were discovered in the peritoneal tissues even after contact with lethal doses of sulfanilamide crystals.

3. Blood sulfanilamide levels determined on patients receiving sulfanilamide intraperitoneally revealed that the maximum blood concentration was attained in three hours, and that for each gram placed intra-abdominally we could expect 1 mg. per 100 c.c. concentration in the blood.

4. In cases of peritonitis we have at hand a precise method for rapidly attaining a desired therapeutic level of sulfanilamide in the blood while establishing immediately at the side of infection a concentration of sulfanilamide impossible to attain by other methods, a concentration adequately bactericidal for some organisms and bacteriostatic for others.

5. The series of cases presented is admittedly small, but we feel with confidence that time will only add to the total increment of cases successfully treated, with no more peril than that associated with sulfanilamide in other fields of therapy. From our observations, we believe that the intraperitoneal use of sulfanilamide is a safe, rational, and effective procedure.

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THE EFFECT OF SULFANILAMIDE CRYSTALS, USED TOPICALLY, ON THE FATE OF TRANSPLANTED BONE

Some Experimental and Clinical Observations

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SULFANILAMIDE and its derivatives are being employed in bone and joint surgery as a prophylactic measure to prevent the relighting, by the trauma of surgical intervention, of a pre-existing, quiescent infection. Indeed, this measure has been suggested as a routine step in surgery of clean bone and joint cases without any history of preceding infection.

Although the use of local chemotherapy has been recommended in bone grafting procedures, the use of the sulfonamide compounds in this field of surgery will depend, among other things, upon proof that these drugs are not deleterious to the normal process of incorporation of a bone graft by the host bone. The purpose of this communication is to offer experimental evidence and some clinical proof that the local use of sulfanilamide in powder form has no adverse effect on the fate of transplanted bone.

EXPERIMENTAL METHODS AND MATERIALS

Eighteen adult rabbits, weighing between 2,000 and 4,000 Grams, were operated upon under ether anesthesia. In 6 animals a graft was removed from one tibia and transplanted to a prepared bed on the opposite tibia, while a graft from the latter tibia was transferred to the former limb. One wound, serving as a control, was closed in layers without the use of any drug locally. The other wound was packed and the bone graft surrounded with sulfanilamide crystals in 4 rabbits and sulfathiazole crystals in 2 rabbits and the wound was closed in layers. In 2 animals the above procedure was pursued without using any drug in either leg. In 2 rabbits, a segment was resected from one ulna and was transplanted to an identical defect in the opposite ulna, and this step was reversed, the radius acting as a splint for the extremity. Sulfanilamide crystals were packed into the wound of one limb, after closure of the opposite control wound into which no drug had been introduced. In 8 rabbits, bone was transplanted from the iliac crest to prepared sites on both tibiae, one leg wound being packed with sulfanilamide crystals in 7 animals and with sulfathiazole crystals in 1 animal, after closure of the opposite control wound into which no drug had been implanted.

Received for publication, Oct. 6, 1941.

The powdered drugs were not sterilized. No postoperative fixation was employed other than firm adhesive dressings. The animals were killed at intervals of one, two, four, six, and eight weeks following operation, and the operated bones were removed, roentgenographed, and examined histologically.

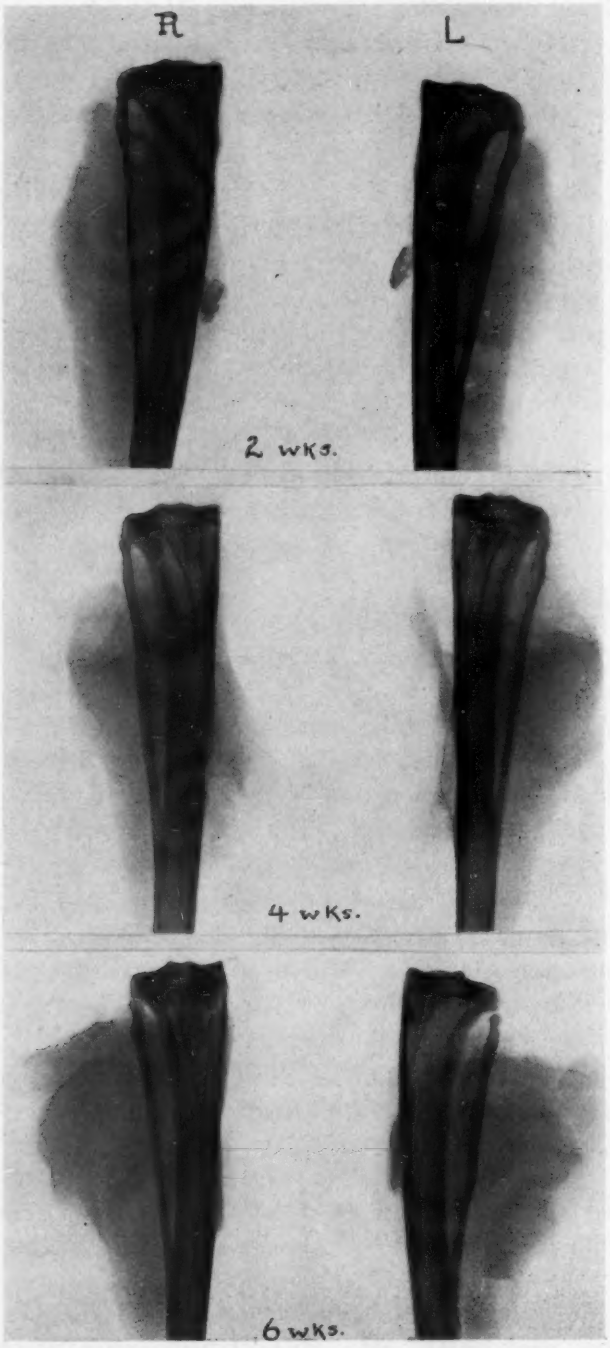
Remarks.—It was my opinion (and this has been held by Key and Burford[1] in their experimental work) that the concentration of the drug was not maintained long enough to affect the fate of the bone graft of the opposite control side wherein no drug had been implanted locally, and that the use of a control in the same animal was preferable to using different animals of approximately the same size, age, sex, and weight. To offset any criticism, however, the experiment was repeated in the tibiae of two rabbits, without using any drug. The features of the incorporation of bone graft by host bone were identical, roentgenographically and histologically, with those in the control legs of the other experimental animals, wherein no drug had been implanted locally.

No effort was made to sterilize the drug and there were no indications, grossly or microscopically, of postoperative infection. This evidence, supported by some clinical experience, suggests that the sulfamido drugs may be sufficiently bacteriostatic not to require sterilization for their local use. Some authors (Key, Frankel, and Burford;[2] Mueller[3]) recommend sterilization of the drug for local use, while others (Stuck, Maxwell, and Monsalvo;[4] Herrell and Brown[5]) consider this to be unnecessary.

Observations.—Roentgenographically, the transplanted bone graft was united to the host bone in both treated and control limbs by the fourth week, although a distinct zone of demarcation was still evident. The graft was well incorporated by the sixth week and by the eighth week it was indistinguishable from the host bone (Figs. 1 and 2).

Grossly, the bone transplant was firmly united to the host bone, in both drug-treated and control limbs, by the fourth week. Histologically, the fate of the bone transplant was identical in the treated and control bones. The main mass of the bone graft was seen to sequestrate and die, except for some viable cellular elements at its periphery. The graft was gradually removed by vascular resorption, slight osteoclastic activity, and the ingrowth of very cellular connective tissue in which new bone was formed. The adjacent periosteal tissues also demonstrated considerable osteoblastic activity. These processes of fibrous tissue invasion, metaplasia, and replacement of dead bone by young living bone occurred concomitantly. Except for isolated fragments of dead bone, the original graft had been almost entirely replaced by the eighth week.

In those wounds where the sulfonamide drugs were implanted locally, the fibroblastic reaction of the paraosseous tissues appeared excessive.



Figs. 1 and 2.—Roentgenograms of the left (sulfanilamide treated) and right (control) tibiae of rabbits that were killed at periods of two, four, six, and eight weeks following operation. In each instance, the bone grafts to the tibiae had been removed from the left iliac crest. While there are slight differences in the roentgenographic appearance of the transplanted bone on the two sides in some of the specimens, due to some variation in the size and integrity of the grafts, the essential features of incorporation of the transplanted bone by the host bone appear to be identical in the drug-treated and control extremities.

This was possibly an expression of reaction to the crystalline foreign substance, although other evidences of foreign body reaction, such as inflammatory cells and giant cells, were not evident. Indeed, crystals of the implanted drugs were not evident in the specimens as early as two weeks postoperatively.

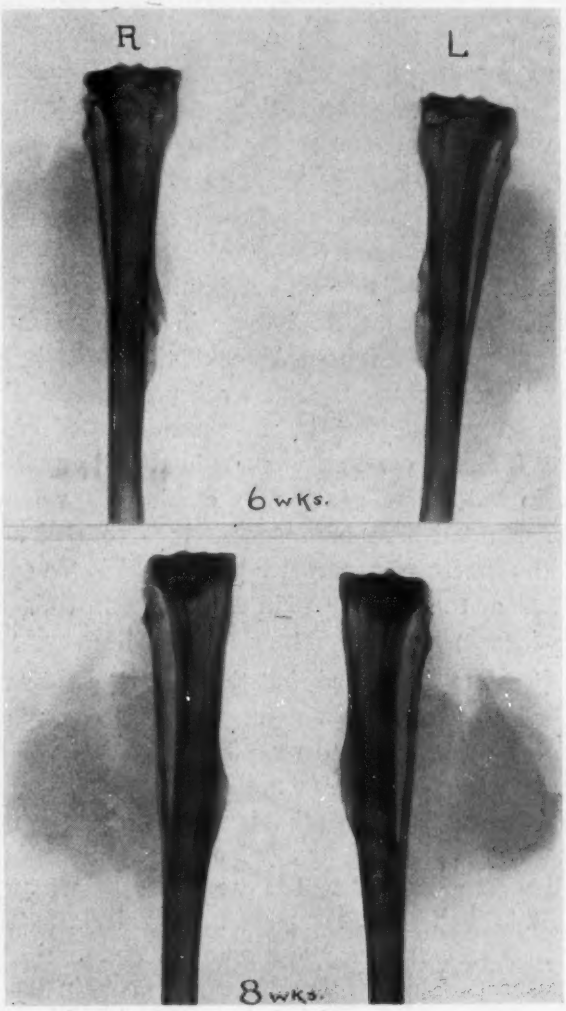


Fig. 2.—See opposite page for legend.

CLINICAL MATERIAL

I utilized sulfanilamide crystals in five patients in whom massive bone grafts were employed. In three of these cases distinct infection was present at the time of operation. One of the three infected patients, a 56-year-old white male, had an extra-articular fusion for a progressively destructive tuberculous arthritis of the wrist, despite the presence of multiple draining sinuses that were secondarily infected with a variety of streptococci and staphylococci. The second patient, a 14-year-old

white male, with a congenitally deformed foot and ankle, gave a history of infection following operation on the affected foot thirteen years previously. During a panarthrodesis procedure, a pocket of pus was exposed, from which a pure culture of *Staphylococcus aureus* was grown. In the third patient, a 51-year-old colored male, the field of a second-stage bone graft for a tuberculous spondylitis was contaminated from a pocket of pus at the upper end of the first graft, which had been inserted four weeks previously. Sulfanilamide was implanted locally in the fourth, potentially infected, case, at the site of a bone transplant for nonunion of the tibia following an infected compound fracture. The fifth case was a clean case without a history of preceding infection, in which a bone graft had been employed for a tuberculous spondylitis.

In all of the cases the operative procedure was completed with primary closure of the wound after local implantation of 4 to 16 Gm. of powdered sulfanilamide (sterilized drug in four patients, unsterilized drug in one). The sulfanilamide level of the blood in each case was maintained by the oral route for one week postoperatively. The infection was completely controlled in the three infected cases and in the one potentially infected case, all wounds healing by primary intention. In the 4 cases in which bone grafts were employed for arthrodesing purposes, the transplanted bone became well incorporated and the fusions were solid by the fourth postoperative month. It is too early to evaluate the ultimate fate of the bone graft in the case with tibial nonunion, but the progress of its incorporation thus far has been most satisfactory.*

Remarks.—It cannot be denied that the fortunate outcome in the three actively infected cases and one potentially infected case might have occurred without the use of the drug. The experience in my five cases, however, corroborates the experimental evidence previously defined and indicates that the local use of the powdered sulfonamide compounds exerts no untoward or deleterious effect on the fate of a bone graft. An extensive, well-controlled trial will be necessary before any reliable conclusions are established as to the merits of local chemotherapy in bone graft surgery. The experience of Campbell and Smith[6] is of limited value in this respect. These authors, in their report in 1940, had reduced the incidence of infection following bone graft procedures in healed compound fractures with latent or potential infection, by the use of the sulfadrugs, from approximately 50 per cent (in a series of 261 onlay bone graft operations performed prior to the use of the drugs) to less than 25 per cent. They failed, however, to record how the sulfonamides had been administered in all of these cases, but it was evident that in some of them the oral route alone had been employed.

*Solid union has occurred in this case. Sterilized sulfanilamide powder has been implanted, locally, at the time of bone-grafting procedures, in two other cases of tibial nonunion following infected compound fractures, without evidence of relighting of the old infection and with satisfactory progress in the incorporation of the transplanted bone by the host bone.

DISCUSSION

The sulfonamide drugs are being employed topically in civil and war surgery, as a powder, solution, or ointment with or without the supplemental use of the drug systemically, in the prevention and active treatment of infections, due to susceptible bacteria, of the skin, mucous membrane, subcutaneous tissue, muscle, bone, viscera, joint spaces, and serous cavities. The local use of these drugs in contaminated or potentially infected fracture wounds has been largely a prophylactic measure (Jensen, Johnsrud and Nelson;[7] Key and Burford;[1] Stuck, Maxwell, and Monsalvo;[4] Campbell and Smith[6]). The topical use of these compounds has been extended to all types of bone and joint surgery where it is feared that a pre-existing infection may be relighted and to extensive procedures where there is considerable damage to the tissues or where metallic foreign bodies are left in the wound (Key and Burford;[1] Key, Frankel and Burford;[2] Campbell and Smith;[6] Key and Frankel;[8] Key[9]). This measure has been utilized as a routine step in clean bone and joint surgery (Key;[9] Key and Burford[10]). The sulfamido compounds are being used locally in the active treatment of acute and chronic bone and joint infections (Key;[9] Dickson, Diveley, and Kiene[11]).

Mode of Action of the Sulfonamide Compounds.—These drugs produce their effect on infections by exercising a bacteriostatic effect on certain susceptible organisms. Their curative action is maximal when (1) the concentration of the drug is high, (2) the local cellular defense is most active, and (3) the concentration of "sulfamide inhibitors" in the wound is minimal (Lockwood[12]). The sulfonamides are, therefore, of greatest value in the prevention of infection.

The topical application of these compounds insures a high local concentration in the tissues. Where the systemic administration of sulfanilamide may produce a concentration of 10 to 15 mg. per cent in the blood and tissue fluids, the local implantation of the crystalline powder of this drug, the most soluble of the sulfamides, makes possible a saturated solution and produces a concentration of 800 to 1,000 mg. per cent (Jensen, Johnsrud, and Nelson;[7] Key and Burford;[1] Stuck, Maxwell, and Monsalvo[4]). This concentration of this drug is not limited to the wound itself but extends into the surrounding tissues and remains constant until the drug is entirely absorbed. This concentration in the wound lasts approximately forty-eight hours; that is, until the drug is completely absorbed and excreted. It is probable that the concentration of sulfathiazole and the other less soluble sulfonamides lasts longer (Key,[9] Key and Burford[10]). The only dangers in the topical administration of the sulfonamides are the possibility of some interference with wound healing and of the uncontrollable toxic reactions in susceptible individuals.

Reactions of Local Tissues.—Although some observers (Thompson, Brabson, and Walker,[13] Mayo and Miller[14]) have felt that healing is stimulated by the sulfonamides, others (Veal and Klepser[15]) have noted

a deleterious effect of powdered sulfanilamide on normal cellular activity. That the local tissues are not inert to this powdered drug is indicated by the pathologic studies on rats by Davis, Harris, and Schmeisser,[16] who observed a local nonspecific foreign body reaction to the crystalline compound. Key and his co-workers[1, 2, 8] observed no untoward effects in their experimental animals of the locally applied sulfonamides on the healing properties of wounds of muscle, subcutaneous tissue, fascia, bone, and joint cartilage. In their clinical experience, however, wounds so treated occasionally did not heal normally, and this was most apt to occur if too much drug had been implanted locally.

In my experimental animals, except for an exaggerated noninflammatory fibroplasia at the site of the transplanted bone, there was no undue foreign body reaction, and incorporation of the bone graft by the host bone progressed at a normal rate. In my limited clinical material, the wounds healed per primam and the progress of the bone graft in the various procedures appeared to be normal.

Absorption of the Sulfonamide Drugs When Implanted Locally.—The blood level is of no great significance in local prophylaxis. It will depend on a number of factors: the amount of drug used, the solubility of the drug, the size of the absorbing surface, the time interval following implantation, and the nature and vascularity of the absorbing surface. Key and Burford[10] made determinations of the blood concentration of sulfanilamide in several patients after local use of this drug in clean operative wounds, and they noted that this concentration varied from 1 to 9.2 mg. per cent (the latter reading having been made where 10 Gm. were implanted locally) on the first and second postoperative days, and that only a trace was present on the third day after operation. They observed a level of from 2 to 4 mg. per cent in the blood when 5 Gm. of the drug were used locally. In my clinical material the sulfanilamide levels dropped rapidly after the initial twenty-four to thirty-six hours and were sustained only by the supplemental oral administration of the drug. My observation is in keeping with the recent studies of Tocantins[17] and of Tocantins and O'Neill;[18] that is, absorption from a bone in which the medullary cavity had been exposed appeared to be more rapid, with an earlier blood level peak and subsequent fall, than when the marrow cavity was not exposed. This would suggest that where the medullary cavity of a bone has been exposed for the reception of or by the removal of a graft, and where the sulfonamides are implanted locally, the local effect should be prolonged by applying a portion of the drug to the overlying soft tissues as they are closed in layers. This would also serve to avoid the too rapid occurrence of a high systemic concentration of the drug.

CONCLUSIONS

The topical application of the sulfonamide compounds as prophylactic bacteriostatic agents in bone graft surgery of potentially infected or

even contaminated cases may serve to insure better anatomical and functional end results over a shorter period of time. The clinical trial of this measure will be dependent upon proof that the sulfonamide drugs, when employed topically, are not deleterious to the normal process of incorporation of transplanted bone by host bone. Experimental observations in eighteen rabbits and a limited clinical experience with five human cases indicate that the local implantation of sulfanilamide crystals has no apparent adverse effect on the fate of transplanted bone.

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THE EMPLOYMENT OF COTTON SUTURE MATERIAL IN THE FIELD

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DURING the maneuvers of the United States Army in North and South Carolina in the fall of 1941, the First Evacuation Hospital† was encamped on a sandy field near Rockingham, North Carolina. A tent hospital of approximately one-thousand bed capacity was erected, wherein medical and surgical care was provided for certain components of the First Army. A large tent was utilized for the housing of all facilities for the performance of major surgical procedures, which were undertaken over a period of forty-six days between October 26 and December 5.

The circumstances under which professional care was administered were presumably comparable in some respects to those which one might encounter in the field in wartime. Patients requiring emergency surgery arrived at the hospital in soiled field clothing after having passed rapidly through clearing stations and other forward echelons. The greater part of the preparation and sterilization of operating room supplies was performed by enlisted personnel, who also acted in the capacities of scrub nurses and circulating nurses. The problems of dust and insect control were considerable. The sides of the operating tent were screened; insecticidal solutions were sprayed throughout the tent at frequent intervals; cardboard compartments were erected within the tent to enclose the operating area. Although these measures were helpful, they did not afford a complete solution to the problem of insect and dust control, and, in spite of vigilance on the part of all operating room personnel, it was not a rare occurrence for a fly to alight upon the Mayo table during the course of an operation.

Inasmuch as circumstances here enumerated were felt to constitute a situation predisposing to wound contamination, considerable speculation arose as to the choice of the most satisfactory suture material.

The selection of cotton as a suture material for most cases was substantiated by the highly encouraging reports of those who had used it in contaminated cases, notably Meade and Ochsner,[1, 2] as well as by the previous experience of both of the writers. Indeed, it is the contention of Meade and Ochsner[2] that the most important use of nonabsorbable suture materials is in grossly contaminated wounds, and they state further that "this contention . . . is based upon the experience that

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Received for publication, Feb. 9, 1942.

the grossly contaminated abdominal wound closed with catgut is particularly likely to disrupt, probably because of two factors: (1) delay in wound healing because of the infection, and (2) early digestion of the suture material by the large amount of proteolytic ferment liberated from the leucocytes. In such an instance the coaptating suture becomes valueless before wound healing has been completed, or, in some instances, even started. If, however, a nonabsorbable suture, particularly cotton, is used, the wound is held intact until infection has subsided and complete healing has occurred." Moreover, in view of the limited nursing facilities which are to be expected in a field hospital, and because of the possible necessity of evacuation of patients over long distances to station hospitals early in convalescence, the added protection of nonabsorbable suture material seemed particularly desirable. Meade and Ochsner[1] have, in fact, made the pointed statement that cotton thread would be a very satisfactory suture in field hospitals in wartime.

During the period of encampment 124 appendectomies were performed. Cotton was employed as the only suture material in every case, with this exception: that fine plain catgut was used for ligation of the appendical stump in most instances in which the stump was inverted. The McBurney incision was used exclusively. There was no mortality in the group.

Cotton was of the ordinary nonmercerized variety, either in black or white. It was sterilized by boiling for 20 minutes or by autoclaving for 15 minutes at 15 pounds pressure, after having been wrapped on spools made of 4 cm. segments of soft rubber tubing. Size No. 80 cotton, usually black, was used for skin closure, while No. 100 white was used for ligation of blood vessels immediately beneath the skin. Either No. 50 or No. 80 cotton was employed in closure of the remaining layers of the McBurney wound, depending upon the individual preference of the operator. Exclusive of the peritoneum, which was always closed with a continuous suture, interrupted sutures were used throughout. Ligation of the mesoappendix was accomplished either with No. 50, No. 20, or No. 8 cotton, the larger sizes ordinarily having been employed when the operator desired to ligate the main bulk of the mesoappendix en masse. In twenty instances the appendical stump was not inverted, either because the operator preferred noninversion or because the extension of inflammatory reaction to the cecum contraindicated such a procedure. Inversion in the remaining 104 cases was accomplished with No. 50 or No. 80 cotton.

Prolonged scrubbing of the abdominal wall with soap and water was adopted as a routine preoperative measure. In cases exhibiting perforation or gangrene of the appendix, as well as in some additional cases where the degree of suppuration was extensive, sulfathiazole or sulfanilamide powder in 8 Gm. quantities was implanted in the peritoneal cavity, although on no occasion was either drug placed in the

wound itself. In every case the wound was subjected to copious irrigation with physiologic saline solution following the closure of each layer.

Of 124 specimens removed, 79, or 63.3 per cent, showed histopathologic evidence of acute suppuration, and 27 of the 79 showed gross evidence of gangrene at the time of removal. There were two instances of perforation (Case 97 and Case 113). In the first instance only local peritonitis was observed, whereas the second was associated with diffuse suppurative peritonitis. In two additional cases (Case 98 and Case 112) gross contamination occurred as the result of disruption in continuity of the wall of a gangrenous appendix during the course of its removal. In each of these four cases a narrow strip of soft rubber dam was placed down to the peritoneum, which was closed. Drains in each instance were removed on the fourth or fifth postoperative day, whereupon each of the wounds in question healed by first intention.

In the remaining 120 cases both the peritoneal cavity and the wound were closed without drainage. Conclusions regarding wound healing in this group are generally based upon a period of postoperative observation of eight days, inasmuch as uncomplicated cases were evacuated to Station Hospitals after elapse of that number of days. Subsequent written communications, however, have been received in 66 instances. In the group of 120 cases there were only four patients (Cases 3, 49, 56, and 78) in whom any variety or degree of wound complication was observed. In three of these (3, 56, and 78) a small collection of uninfected serous fluid was evacuated from the wound on one occasion only, for each case, whereafter it did not reappear. It is felt that these cannot be regarded as instances of wound infection. The one remaining patient (Case 49) developed a left femoral thrombophlebitis on his sixth postoperative day, and suffered disruption of his wound on the thirteenth postoperative day. Following the evacuation of a large quantity of purulent material, the wound healed by granulation. The incidence of wound infection, assuming this to be the only instance which can be so regarded, is 0.83 per cent in the series of 120 cases, and the incidence of wound complication of any sort, regardless of nature or degree, is 3.33 per cent.

In one patient (Case 70), regarding whom no specific mention has heretofore been made, there developed on the fifth postoperative day sudden evidence of generalized peritonitis, in consequence of which his abdomen was reopened at the site of his previous wound. It was apparent that an abscess had formed about the appendical stump (which had not been inverted) with subsequent rupture of the abscess into the general peritoneal cavity. The peritoneum, however, was sealed, and the appearance of the wound at the time of its re-entry was clearly that of primary healing. Convalescence and wound heal-

ing were uneventful following drainage of the abscess. No attempt was made to remove the cotton sutures which had been introduced at the first operation.

COMMENT

Because of our fear of increased incidence of postoperative pulmonary complications arising from the nature of our accommodations, the general policy was adopted of allowing patients to be out of bed on the second or third day following operation. No ill effects of any sort were observed therefrom. We should not have been able to permit such early locomotion with equal assurance had we not enjoyed the sense of added security arising from the use of nonabsorbable suture material. As a corollary to this it may be suggested that an analogous situation exists when it is necessary for soldiers who have been operated upon in the field of combat to be evacuated considerable distances by motor over rough terrain to hospitals in the rear echelons.

It is not to be presumed that the gratifyingly low rate of wound infection and wound complication achieved under circumstances tending to favor wound contamination is to be ascribed to the nonirritant features of cotton sutures alone. On the contrary, we were of the opinion that careful preoperative skin cleansing and copious irrigation of wounds were of primary importance in promoting uncomplicated wound healing.

Our experiences with cotton suture material are in entire support of the contentions of Meade and Ochsner, that cotton may be employed safely in clean, contaminated, or infected wounds. We encountered no evidence to indicate that cotton acts as a detriment to wound healing in any way. Similar conclusions have been reached by Thorek,[4] Guthrie,[5] Farris,[6] and Cannaday.[7]

Finally, of less importance but of sufficient significance to justify its mention, cotton possesses the additional advantages of being inexpensive, plentiful, easy to carry, and easy to sterilize. Meade and Long[3] state that the average cost of cotton in 100 surgical procedures was 1¼ cents per case, whereas the cost of catgut, as computed from a series of 469 operations, was $1.16 per case.

CONCLUSIONS

Cotton suture material has been employed in 124 consecutive appendectomies performed in a tent upon soldiers engaged in field maneuvers simulating warfare. The results obtained therein are regarded as a reasonable basis for the conclusion that cotton is a satisfactory suture material for field use in clean, contaminated, or infected wounds.

The authors wish to acknowledge their gratitude to the Army Medical Museum for the examination of pathologic specimens, and to the members of the Surgical Service of the First Evacuation Hospital Reinforced for their assistance in all phases of the clinical work.

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THE USE OF ESTROGENIC SUBSTANCES IN THE PREOPERATIVE AND POSTOPERATIVE TREATMENT OF HYPERTHYROIDISM

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THE use of estrogenic substances in conjunction with the surgical treatment of hyperthyroidism has previously been discussed by one of us (A. H. S.).[1] As indicated in that brief report, employment of this form of therapy was based upon inhibiting the secretory activity of the anterior lobe of the hypophysis, thereby reducing the production of anterior pituitary thyrotropic hormone, a mechanism suggested by Sherwood and Bowers,[2] and later by Grumbrecht and Loeser.[3]

The low blood concentration of thyrotropin which has usually been found to exist in hyperthyroidism[4-11] implies that considerable improvement would not accompany a further reduction of thyrotropic hormone levels, and that any good effects following estrogen therapy are probably not the result of inhibition of thyrotropin production. However, not only has it been found[12] that in hyperthyroidism there is sometimes an increase in the amount of thyrotropin in the blood, but Starr and Patton[13] have shown that in hyperthyroidism there is an increased sensitivity to thyrotropin.

Because a lowering of basal metabolism was observed following the administration of estrogen to thyroidectomized animals, Sherwood[14] has concluded from his more recent studies that the basal metabolism lowering effect of estrogenic substances is due to a direct hormone antagonism in the tissues rather than to either a direct influence on the thyroid gland, or mediation through the pituitary gland and the anterior pituitary thyrotropic hormone. However, entirely apart from the beneficial effects which a lessening of thyrotropic hormone production might have by retarding stimulation of the thyroid gland, reduction of the direct metabolism-stimulating effects produced by certain pituitary extracts[15-22] is an additional mechanism whereby inhibition of pituitary secretion might contribute to the beneficial effects of estrogen therapy in hyperthyroidism. These latter findings, along with those[23-25] concerning the pituitary-thyroid relationship or the thyroid-stimulating effect of anterior pituitary thyrotropic hormone, coupled with the demonstrations[14, 36-38] of the basal metabolism-lowering effect of estrogenic substances in experimental hyperthyroid animals, constitute a rational basis for the administration of estrogen in conjunction with the surgical treatment of patients with hyperthyroidism.

Received for publication, Nov. 24, 1941.

Additional inferences which might be drawn from clinical observations concerning thyroid-pituitary-ovarian relationships at puberty, in pregnancy, in castrates, and at the menopause, as well as in obesity, Cushing's disease, Simmonds' disease, acromegaly, myxedema, and hyperthyroidism are not included in this brief report.

Collateral estrogen therapy would seem to be especially appropriate when hyperthyroidism is severe, when there is unsatisfactory response to the usual methods of preoperative preparation, and during the intervals between multiple-stage operations. This report presents what are considered to be some significant favorable effects observed in five cases which received this supplementary therapy.

Description of Cases Receiving Estrogen Therapy.—The five patients to whom estrogen therapy was given had diffuse hyperplastic goiters and were selected to receive estrogen therapy either because of extreme toxicity or because they had shown no improvement following the usual preoperative preparation. In each case, subtotal thyroidectomy was performed by the same surgeon (A. H. S.). In three cases the operation was done in a single stage, while in two cases a two-stage operation was performed. Two of the patients had received iodine elsewhere for some time preceding hospital admission, and were considered to be iodine-fast. In addition to estrogen therapy, preoperative preparation included bed rest; Lugol's solution, minims 10 to 15 t.i.d.; sodium bromide sedation; a high caloric diet; calcium gluconate, gr. 15 t.i.d.; and large doses of vitamins A, B_1, or B complex, C, and D. Three of the patients had a fulminating type of hyperthyroidism. The average basal metabolic rate in estrogen-treated cases was +57 per cent (Fig. 1). The average pulse rate on admission was 114 beats per minute (Fig. 4). Of the five patients, four were females.

Control Cases.—Seven patients with hyperthyroidism who received the same basic preoperative treatment, with the exception of estrogen therapy, and who were operated upon by the same surgeon (A. H. S.), have been studied and constitute a basis for the comparison shown in the accompanying graph. Of these patients, three had diffuse hyperplastic goiters, and four had nodular goiters. The average basal metabolic rate in the control group was +41 per cent (Fig. 1) and the average pulse rate on admission in the control cases was 102 beats per minute (Fig. 4).

Estrogenic Substances Used, Including the Amounts and Methods of Administration.—The estrogenic substances used were theelin in oil administered intramuscularly, supplemented in one case by diethylstilbestrol, administered by mouth. On account of uncertainty concerning the effects of estrogenic substances when administered to patients with hyperthyroidism, the doses in the first cases were small, as indicated in the following summary.

CASE 1.—Doses of 2,000 estrogenic units of theelin in oil were administered daily for six days preceding operation.

CASE 2.—In this case, thyroidectomy was done in two stages. Doses of 10,000 estrogenic units of theelin in oil were administered on the day preceding the first stage. Preceding the second stage, 10,000 estrogenic unit doses of theelin in oil were administered for three days.

CASE 3.—This patient received theelin in oil, 10,000 estrogenic units daily, for two days preceding operation.

CASE 4.—Theelin in oil, 10,000 estrogenic units, was administered daily for three days preceding operation.

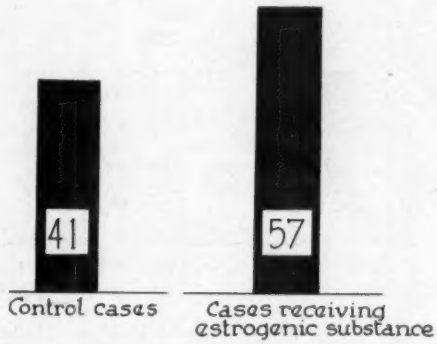

Fig. 1.—Graphic representation of the average basal metabolic rates on admission of the control cases, and of those selected to receive estrogenic substances. The higher average metabolic rate in the latter group was paralleled by signs and symptoms of greater toxicity.

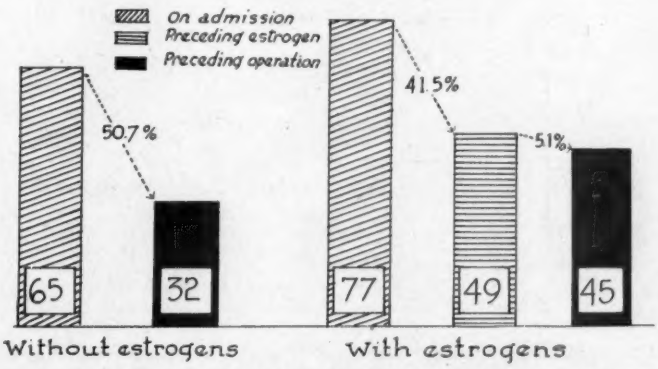

Fig. 2.—Chart showing the reduction in the average basal metabolic rate during the preoperative period in the three most toxic patients in the control group, compared with that in the three most toxic patients who received estrogen therapy.

CASE 5.—In this case operation was done in two stages. Theelin in oil, 10,000 estrogenic units, was administered daily for two days preceding the first stage. Following the first stage, 4 mg. of diethylstilbestrol were given by mouth during the first twenty-four hours following operation, and 1 mg. was given during the second twenty-four-hour postoperative period. Theelin in oil, 10,000 estrogenic units, was also administered daily for two days preceding the second-stage operation.

Results.—Fig. 2, which is based on the three most toxic cases in the group receiving estrogen therapy, and on the three most toxic cases in the control group, shows the comparative reductions in the average basal metabolic rate during the preoperative periods in the control cases and the cases which were selected to receive estrogen therapy. The refractoriness to usual preoperative therapy in the latter group is clearly shown, and the additional lowering of basal metabolic rate following estrogen therapy, although not great, may be considered to be somewhat significant.

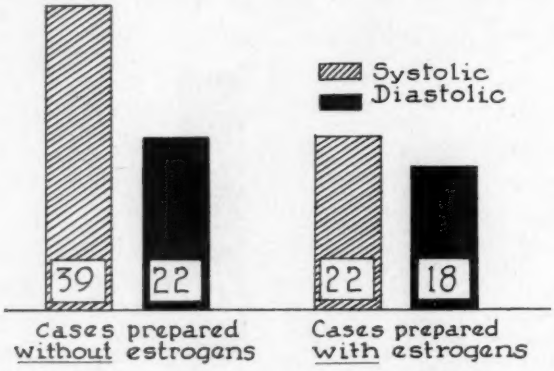

Fig. 3.—Chart showing the average variations in blood pressures during operation in those patients who received only ordinary preoperative preparation, compared with those patients who also received estrogenic substances.

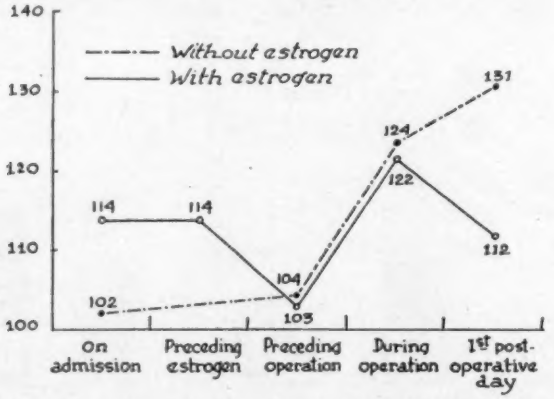

Fig. 4.—Graph showing average pulse rates in the estrogen-treated cases compared with those in the control group, on admission, in response to preoperative treatment, during operation, and on the first postoperative day.

The average variations in blood pressures during operation are shown graphically in Fig. 3, which demonstrates that fluctuations in both systolic and diastolic blood pressures during operation were less in the estrogen-prepared group of cases.

The average pulse rates in the estrogen-treated cases compared with those in the control group at the time of admission, in response to preoperative treatment, during operation, and on the first postoperative day, is indicated in Fig. 4. Although the average pulse rate in the cases

which received estrogen therapy remained elevated following the basic treatment employed in all cases, the administration of estrogen was followed by a fall in pulse rate to approximately the same level reached by the less toxic control cases. Whereas the average pulse rate during operation was practically the same in both the estrogen-treated and control groups, the average pulse rate on the first postoperative day was much lower in the cases which received estrogens.

In addition to the graphic demonstrations of the favorable effects apparently produced by estrogen therapy, as shown in Figs. 2, 3, and 4, other objective evidences of beneficial effects of estrogen therapy included improvement in respect to nervousness, apprehensiveness, and purposeless movements. Accompanying subjective improvement was evidenced by the greater feeling of well-being experienced by the estrogen-treated patients during the preoperative period. Furthermore, the postoperative courses of the patients treated with estrogens were remarkably smooth.

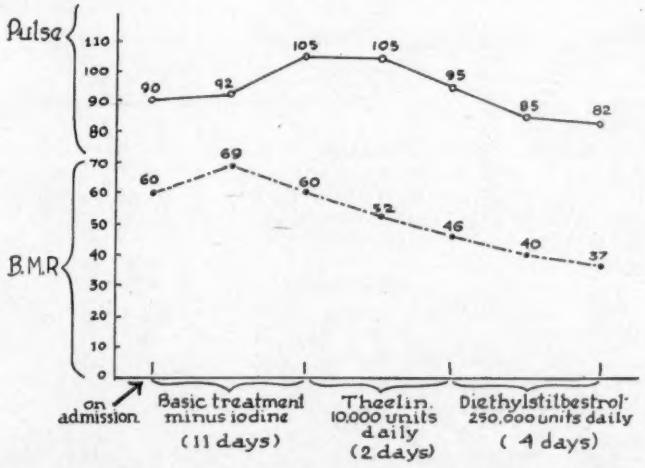

Fig. 5.—Graph showing the changes in basal metabolic rates and pulse rates, in a patient not included in the present comparative analysis, following the administration of relatively large doses of estrogens. Continued administration of diethylstilbestrol for several days following the period shown in this graph was associated with a rise in the rates, suggesting that refractoriness to estrogen therapy may occur. This patient was subsequently given iodine, and the subtotal thyroidectomy which was later done was followed by an uneventful recovery.

DISCUSSION

Because of the uncertainty of the effect of estrogen therapy in spontaneous hyperthyroidism in the human being, there was considerable variation in the amount and the timing of the doses of estrogenic substances. After observing the apparent benefit and the absence of undesirable reactions when small doses were administered, larger doses were subsequently employed. In this small group of cases it was impossible to establish any significant relationships between the amounts of estrogenic substances administered and the beneficial effects observed.

Further observations are presently in progress concerning the effect of diethylstilbestrol and monomethylstilbestrol given in various amounts and according to different dose schedules. Fig. 5 shows the changes in basal metabolic rates and pulse rates, in a patient not included in the present comparative analysis, following the administration of relatively large doses of estrogens. Continued administration of diethylstilbestrol for several days following the period shown in this graph was associated with a rise in the rates, suggesting that refractoriness to estrogen therapy may occur. This patient was subsequently given iodine, and the subtotal thyroidectomy which was later done was followed by an uneventful recovery.

CONCLUSIONS

From observations in a small group of cases with hyperthyroidism, selected either because of their failure to respond to the usual preoperative preparation, or because of the severity of the disease, the administration of estrogenic substances in conjunction with both single and two-stage thyroidectomies appears to be beneficial.

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SKELETAL MANIFESTATIONS OF THYROID DISEASE

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DISEASES of the thyroid gland not infrequently have skeletal manifestations of great significance. Neoplasms of thyroid origin, hypo- and hyperthyroidism are commonly associated with changes in the osseous structures, which, however, are not often recognized clinically, except in those cases of bone metastases from carcinoma of the gland. A review of the literature and a description of six cases which we have observed have been undertaken in order to illustrate the various changes.

NEOPLASMS

Neoplasms of the thyroid gland may arise from any of the germinal layers. Mesenchymal tumors are quite rare. Those arising from the endothelium are the most common. According to Simpson, 4 per cent of all goiters without exophthalmos are carcinoma. In a series of 238 cases of carcinoma of the thyroid, Erhardt[8] found the following metastatic distribution: lung, 129; bones, 66; liver, 36; kidneys, 20; pleura, 16; and brain, 12. The order of frequency of bone involvement was: skull, vertebrae, pelvis, sternum, and femur.

Thyroid tissue has been found in almost every bone of the body. It consists of tissue which has the microscopic anatomy of normal fetal or adult thyroid gland, some appearing benign and others malignant. In either case it is easily demonstrated that the thyroid struma has invaded normal bone structure and replaced it by first destroying it. In cases where malignancy is found, the primary focus is usually found in a carcinomatous thyroid gland. This type of case is easily diagnosed and causes little confusion. The involved bone presents rarefied areas at the sites of metastases on roentgenograms.

CASE 1 (Hosp. No. 61672).—O. F., a 34-year-old white male, was admitted on Nov. 11, 1936, with the chief complaint of sudden, sharp, stabbing pain in the anterior neck, aggravated by deep breathing and associated with dyspnea. He also complained of pain above the right eye. The total duration of the complaints was four months. One year previous to this admission the patient had been at another hospital from which a report indicated that he had had a partial resection of a carcinoma of the thyroid because of pressure symptoms. Pulmonary metastasis had been demonstrated at that time. During this admission roentgenograms showed involvement of the right upper lobe of the lungs and three rarefied areas of the parietal bone along the vertex (Fig. 1). On Dec. 5, 1936, the patient was discharged unimproved. No follow-up was obtainable.

CASE 2 (Hosp. No. 58253).—R. S., a 65-year-old white female, entered the Hospital for Joint Diseases on April 13, 1936, because of weakness and a mass

Received for publication, Aug. 5, 1941.

in the neck which she had had for fifteen years. The thyroid was replaced by a very hard mass, approximately 10 cm. by 6 cm., extending under the right sternomastoid muscle and adherent to it. X-rays showed two metastatic deposits in the right middle lobe of the lung. Basal metabolic rate was plus 15 per cent.

Because of pressure symptoms on the trachea, the mass was removed on April 25, 1936. The patient failed steadily after operation and died May 3, 1936, eight days after operation, from cardiovascular failure. Postmortem examination revealed an anaplastic carcinoma of the thyroid gland which had metastasized to the lungs, pleura, pericardium, hilar lymph nodes, and sternum. The metastasis to bone showed the typical replacement by destruction.

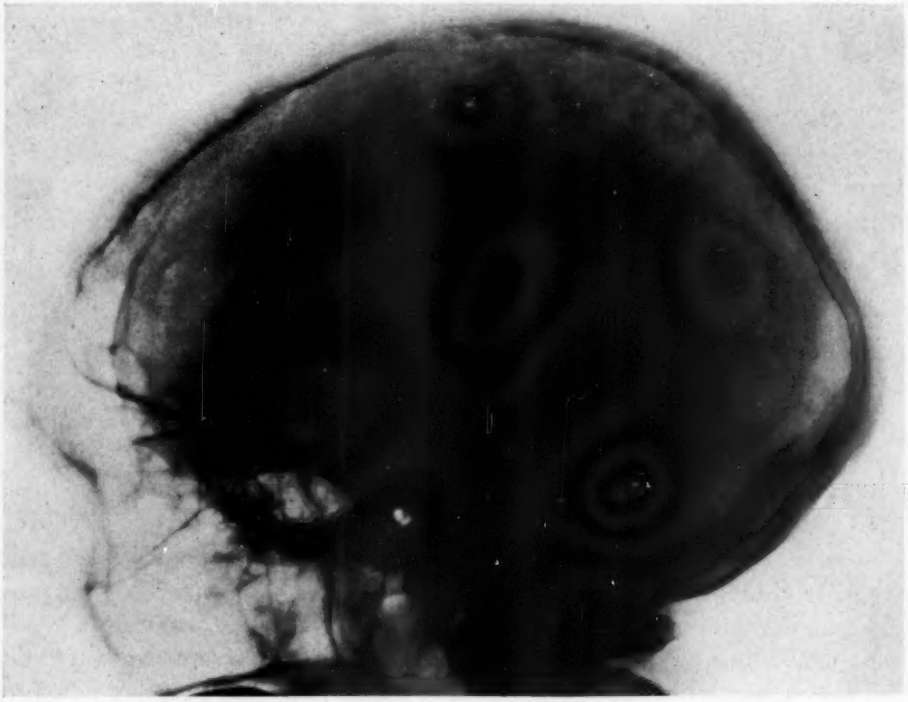

Fig. 1.—Patient O. F. Arrows indicate osteoporotic areas in the parietal bone.

The situation becomes increasingly complicated where thyroid tissue is found in bone without any evidence, clinically, of involvement of the thyroid gland itself. The pathology of replacement by bone destruction is the same as presented in the preceding cases. This group of cases may be subdivided into two types: (1) benign, and (2) malignant. The benign lesion is considered by some authorities to consist of aberrant thyroid tissue from misplaced embryonic rests. The malignant group may be further classified into: (1) malignant degeneration of aberrant thyroid tissue, and (2) metastasis from a thyroid gland which has at some time borne a carcinoma.

"Benign" thyroid neoplasms in bone may be aberrant misplacements or "benign" metastases, capable of assuming malignant potentialities. This is still a heated point of controversy. Pathologic reports

by Douglas Symmers from two cases described by Kaplan[10] demonstrate the first theory. Symmers believes that aberrant thyroid tissue may be found in regions away from the head and neck. In the first case the pathologic report reads: "Thyroid tissue showing in places rather high alveolar epithelium . . . otherwise thyroid shows no noteworthy histological changes from the normal. There is nothing in the tissue to suggest malignancy. It undoubtedly represents aberrant thyroid tissue such as has not infrequently been described in various parts of the body including the meninges." In the second case Symmers reported: "Microscopic examination shows the presence of characteristic thyroid tissue . . . in other words, the histology of the mass . . . shows the presence of thyroid tissue which does not depart noticeably from that picture which perhaps might be considered normal. There is certainly nothing whatsoever in the tissue to indicate histologically any sign of malignant transformation. In other words, it seems to be an established fact that there are those growths which are histologically benign but which nevertheless are capable of malignant behavior in that they set up secondary deposits in distant structures." Cruickshank[5] favors the theory of benign metastasis and we quote from his writings: "A normal thyroid, a colloid thyroid, a thyroid containing a small adenoma, a thyroid containing a malignant adenoma, each has at some time or the other been reported as having produced a metastasis consisting of normal thyroid tissue. The clinical fact or observation remains that tumors identical with normal thyroid tissue do occur in bones of patients who present no apparent abnormality of their thyroid glands."

The most recent explanation of these diverse findings has been offered by I. Levin.[11] He concludes that there is either a favorable or an unfavorable medium for growth of cancer cells and that bone is a good medium. Normal thyroid tissue, however, is relatively resistant to growth of cancer cells. It is for this reason that the paradox of thyroid tumor metastasis to bone exists with no evidence of malignancy in the thyroid itself. Furthermore, so-called aberrant thyroid tissue existing as a metastatic deposit from a thyroid neoplasm, may assume malignant potentialities when located in a good "culture medium" such as bone.

Whenever a rarefying bone lesion is found, other diagnostic possibilities in addition to thyroid neoplasms also arise. Multiple myeloma, endothelioma, and hyperparathyroidism may produce a similar picture. The distinguishing differential points are to be found in the accompanying table.

One other characteristic sometimes found in thyroid deposits in bone should be borne in mind. Several cases of pulsating tumors over bony regions have been reported in the literature with thyroid neoplasm as the culprit.[4] To make a preoperative diagnosis in these cases is extremely difficult since the lesion more frequently resembles an aneurysm,

TABLE I

DISEASE	SYMPTOMS	BONES INVOLVED	X-RAY	BENCE-JONES	BLOOD CA., P.	PHOSPHATASE	CA., P. BALANCE
Thyroid tumors	Pain	Ribs, spine, skull, femur, humerus	Destruction with no new growth. Pathologic fracture may occur	Positive if marrow involved	Normal	Usually high	Normal
Multiple myeloma	Pain	Multiplicity of flat bones, as a rule	Small circumscribed lesions. Rarefaction; thinning of cortex	Positive	Normal	Normal	Normal
Endothelioma	Pain	Multiplicity and all bones may be involved	Peculiar longitudinal striated appearance of shaft with signs of invasion and no bone formation	Negative	Normal	Normal	Normal
Hyperparathyroidism	Pain in supporting bones. Hypotonia, nausea, vomiting, cramps. Polyuria, polydipsia due to increased excretion of Ca. and P.	Long tubular bones, pelvis, skull, jaw, ribs	*Early:* osteoporosis *Late:* single and multiple cysts in medulla and beneath periosteum. Also bowing, coxa vara, flattening of pelvis, miliary granular type of osteoporosis	Negative	High Ca. Low P.	High	Negative balance

an angioma, a meningocele, a hematoma, or some other highly vascular tumor.[4] In 1930 Wilkens[20] reported a patient who he first thought had an arteriovenous aneurysm. Frozen section at the time of the operation showed tissue not unlike fetal adenoma of the thyroid. Cruickshank[5] in 1938 presented another case of pulsating tumor due to thyroid metastasis to bone. The preoperative diagnosis was meningocele. The postoperative diagnosis was gumma or sarcoma. Pathologic examination was necessary in order to make a final diagnosis.

The differential diagnosis of pulsating tumors revolves about two important points: (1) a decision must be made as to whether the lesion is benign or malignant, and (2) the absence of a thyroid lesion or a long interval of many years between an excised thyroid gland neoplasm and a pulsating tumor of bone may be misleading.

Aneurysms or angiomata show slow clinical progress. The progression of symptoms in malignant, pulsating, metastatic thyroid lesions of bone is rather rapid. In the latter, roentgenographic evidence of bone destruction and the rapid development of neurologic signs are much more common. The diagnosis is finally confirmed by exploration and histologic examination.

It has also been said[8] that 50 per cent of thyroid metastatic bone malignancies have symptoms of hyperthyroidism. Removal of the primary lesion rarely produces changes in the symptoms but removal of the secondary growth might give rise to myxedema.

Our third case report is very interesting since it combines a number of illustrations of the features already brought forth. It demonstrates the long interval between primary and secondary lesion; it is illustrative of the controversial arguments as to the origin of the secondary lesion; it demonstrates pulsating tumors of thyroid metastatic origin with differential features of diagnosis; it shows hyperthyroidism as a result of thyroid metastatic deposit in bone, since removal of the secondary lesion gave marked relief from thyrotoxic symptomatology.

CASE 3 (Hosp. No. 79401).—B. B., a 45-year-old white male, was admitted to the Hospital for Joint Diseases on three different occasions. His first admission, in 1938, was for pain in the right shoulder, which was diagnosed as arthritis and treated by immobilization. In 1939 he was admitted for symptoms of hyperthyroidism, notably tremor, weakness, and loss of weight. At that time he stated that he had had a thyroidectomy in 1923 at a Cleveland hospital because of "over active goiter." The left lobe of the thyroid was apparently enlarged and basal metabolic rate was plus 24 per cent. He was given medical treatment for hyperthyroidism and discharged, four weeks later, improved and with basal metabolic rate plus 10 per cent.

In October, 1939, he returned to the hospital complaining of severe pain in the lower back radiating to the lower extremities. Onset was sudden, one week previously, and progression of the intensity of pain was rapid. His symptoms of hyperthyroidism had also recurred and become marked. The striking feature of the physical examination was the presence of a mass in the region of the spinous

processes of the eleventh and twelfth dorsal vertebrae (Fig. 2). The tumor measured about 4 cm. in diameter and pulsated synchronously with each cardiac systole. Radiographs showed an absence of the spinous process of the eleventh dorsal vertebra (Fig. 3) and of the descending articular process of the twelfth dorsal vertebra (Fig. 4). Other x-rays of the spine, after injection of opaque fluid, demonstrated a midline tumor which was highly vascular and encroached on the spinal canal.

Fig. 2.—Patient B. B. Photograph of patient showing the location of the pulsating tumor.

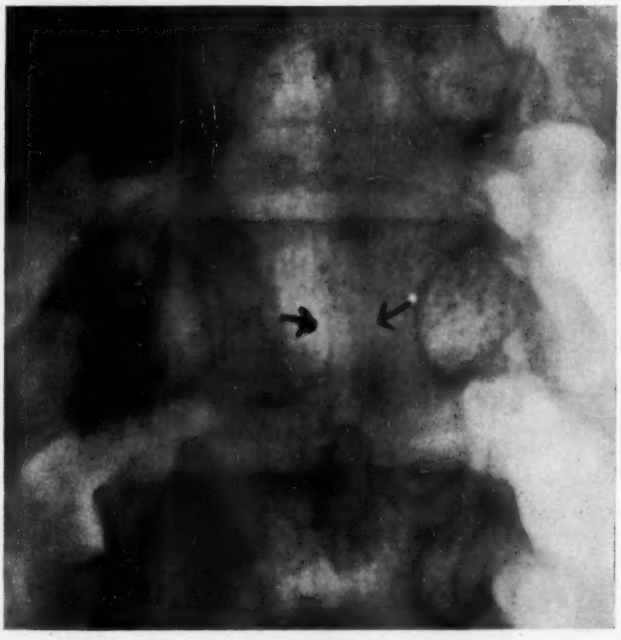

Fig. 3.—Patient B. B. Roentgenogram showing absence of spinous process of the eleventh dorsal vertebra.

Two basal metabolic rates were plus 27 per cent and plus 46 per cent. The fasting blood sugar was 89 mg. per cent, the serum calcium 10.6 mg. per cent, the serum phosphorus 3.3 mg. per cent. The serum phosphatase was elevated to

9.9 Bodansky units. The urinary Bence-Jones reaction was negative. The provisional preoperative diagnosis was an aneurysm.

One observer palpated a firm hard nodule in the left sternomastoid muscle. He was of the opinion that this might be the primary site of the neoplasm producing a metastasis to the back. Other diagnoses were osteolytic sarcoma and hemangioma.

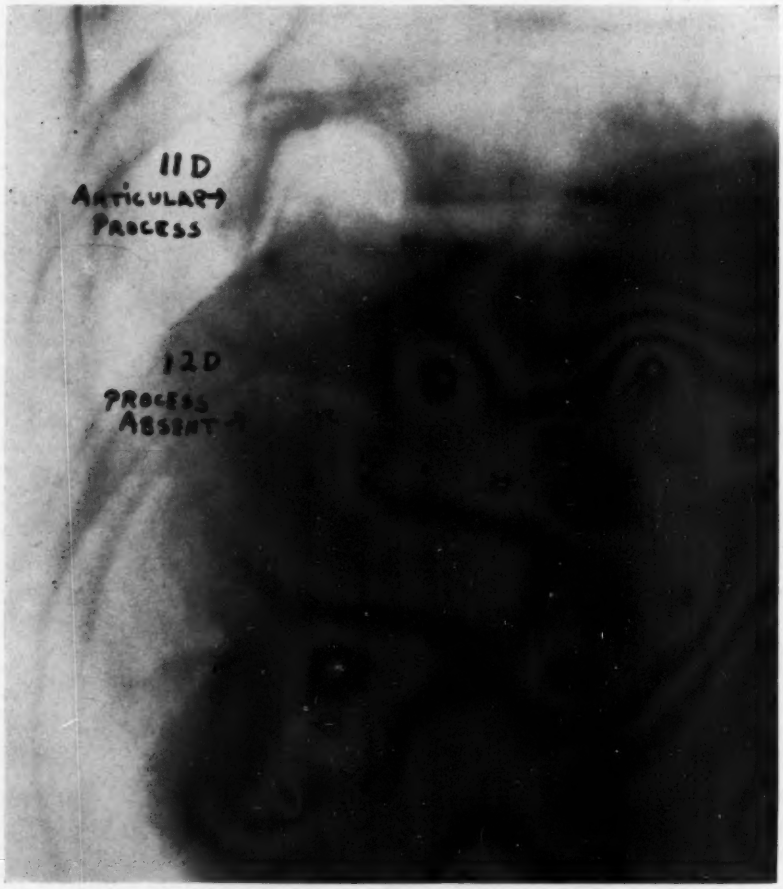

Fig. 4.—Patient B. B. Lateral roentgenogram showing the absence of the descending articular facet of the twelfth dorsal vertebra.

On Nov. 9, 1940, an exploratory operation was performed. A circular tumor about 3.5 cm. in diameter was found deep in the fascia. It completely destroyed the spinous process of the eleventh dorsal vertebra. The entire tumor together with the laminae of the twelfth dorsal and the first lumbar vertebrae were removed. It was then seen that the tumor did not involve the dura. Pulsations were noted, but so far as could be determined, they seemed to be transmitted to the tumor from the deeper structures. The exact nature of the tumor could not be determined at that time. The diagnosis, therefore, remained in doubt until the histologic examination was completed. This showed numerous areas of thyroid tissue with replacement by papilliferous adenocarcinoma (Figs. 5 and 6). This diagnosis was substantiated by a later report from the St. Vincent's Charity Hospital of Cleveland, which indicated that at the time of the thyroidectomy in 1923 a malignant adenoma had been found.

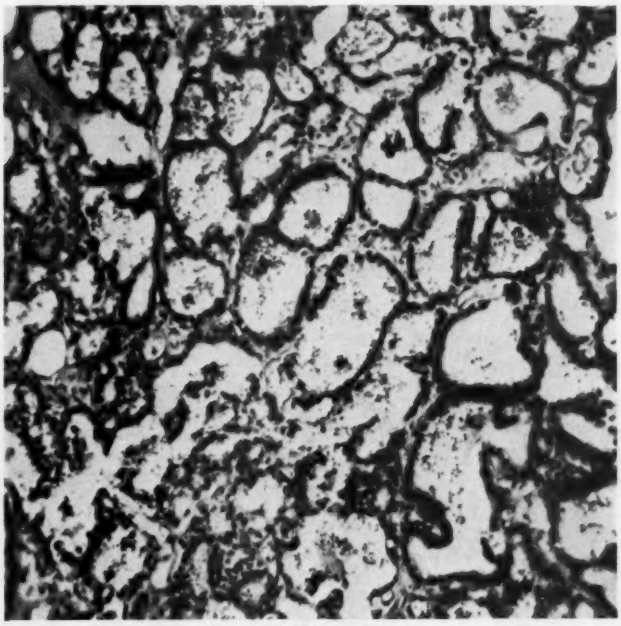

Fig. 5.—Patient B. B. Low power microphotograph of the tumor. This shows the papilliferous nature of the adenocarcinoma with the tendency toward formation of thyroid acini.

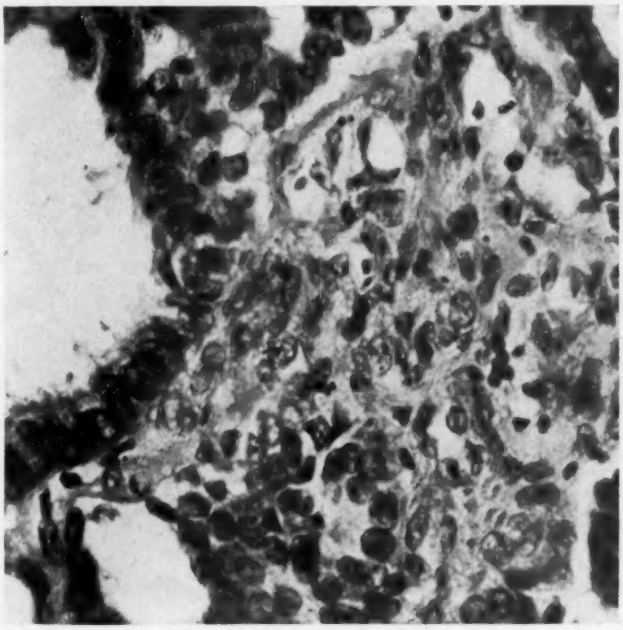

Fig. 6.—Patient B. B. High power magnification showing invasion of connective tissue by carcinoma cells.

The mass noted in the sternomastoid muscle was removed but showed no thyroid tumor nor evidence of adenocarcinoma. The patient's further course was uneventful and the hyperthyroid symptoms lessened. When last seen in October, 1940, there was no recurrence.

HYPOTHYROIDISM

Skeletal changes of hypothyroidism are of three main varieties: (1) deficient growth in the young due to absence of, or retardation in, centers of ossification; (2) retardation of osteoid tissue replacement and ossification in adults; and (3) abnormal changes in the epiphyseal plate and epiphyses (juvenile chondroepiphysitis). The first group is not being considered in this review.

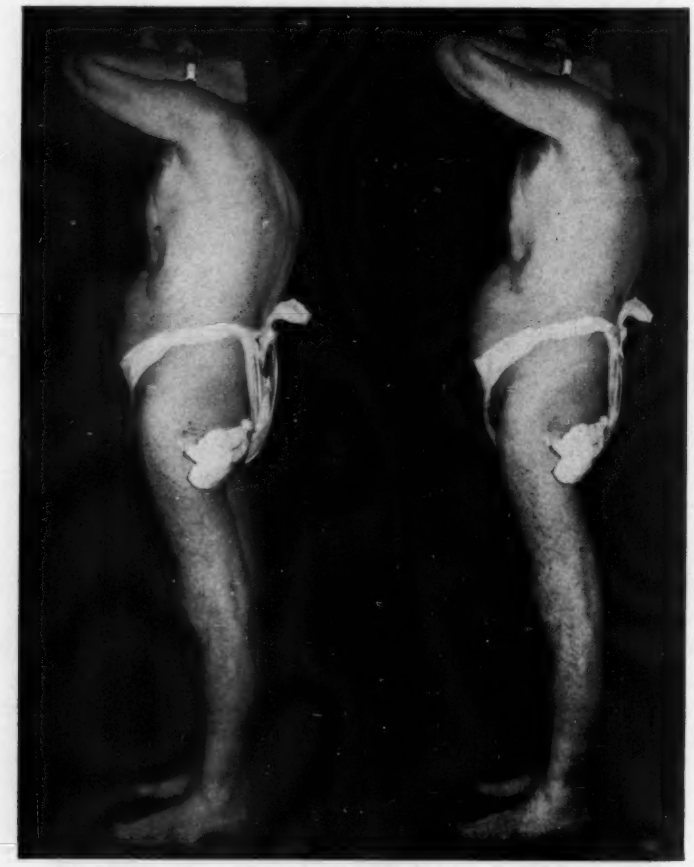

Fig. 7.—Patient M. D. Photograph showing the curve of the back with gibbus formation.

It has been commonly believed that when hypothyroid changes have their inception in adult life no skeletal changes result. This is true in a large majority of cases. However, hypothyroidism is manifested by a generalized metabolic disorder in which all of the endocrines play an important part. To absolutely link such hypothyroidism to any

skeletal change is very difficult. Nevertheless, skeletal disease unaccounted for except by the presence of hypothyroidism may be deemed to be a resultant of a combination of forces in a generalized disordered metabolic process. The pathology consists of a lack of replacement of resorbed bone by osteoid tissue and its ossification, just as cells of any soft tissue replace those which die. The following report presents a patient with severe skeletal changes in whom an exhaustive investigation revealed only a hypothyroid state. This patient did not respond to orthopedic management alone, but a period of thyroid management produced a satisfactory response.

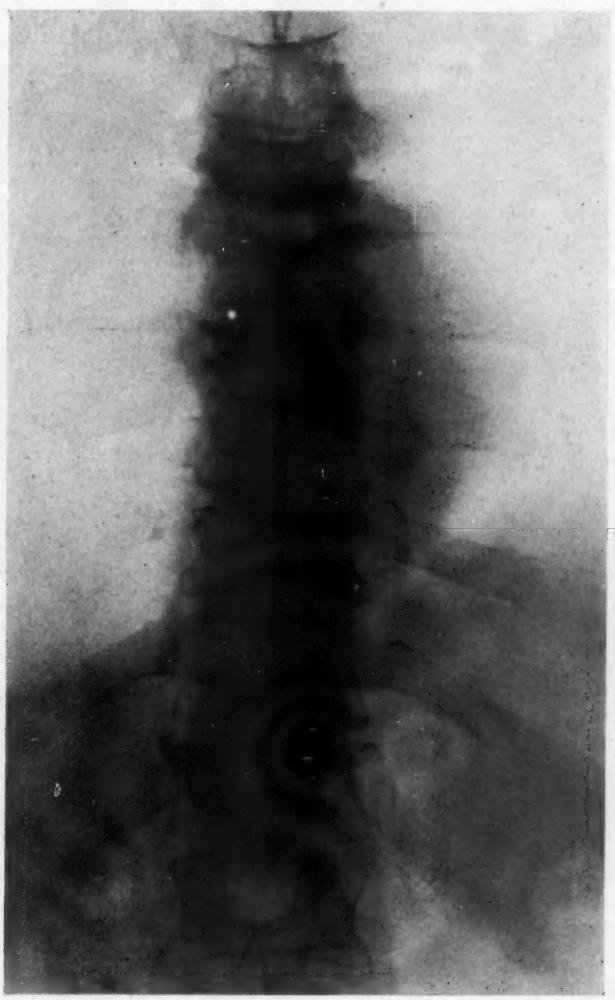

Fig. 8.—Patient M. D. Roentgenograms of the dorsal spine in the anteroposterior view showing compression of the bodies of the sixth, seventh, and eighth dorsal vertebrae.

CASE 4 (Hosp. No. 73953).—M. D., aged 46 years, was admitted on Dec. 9, 1938, with a five-week history of pain in the back, "crushing and tearing" in character. The significant finding on physical examination was the patient's pos-

ture, which was notable for the sweeping flexion curve along the entire spine, with the greatest curvature in the dorsal region and gradual gibbus formation at about the level of the ninth and tenth dorsal vertebrae (Fig. 7). Pain was pronounced on either flexion or extension of the spine. Radiographs revealed marked compression of the bodies of the sixth, seventh, and eighth dorsal vertebrae with widening of the intervertebral spaces (Figs. 8 and 9). Most significant was the absence of evidence of a destructive process. The skull plate presented a moderate degree of osteoporosis. X-ray interpretation was that of a disordered metabolic process.

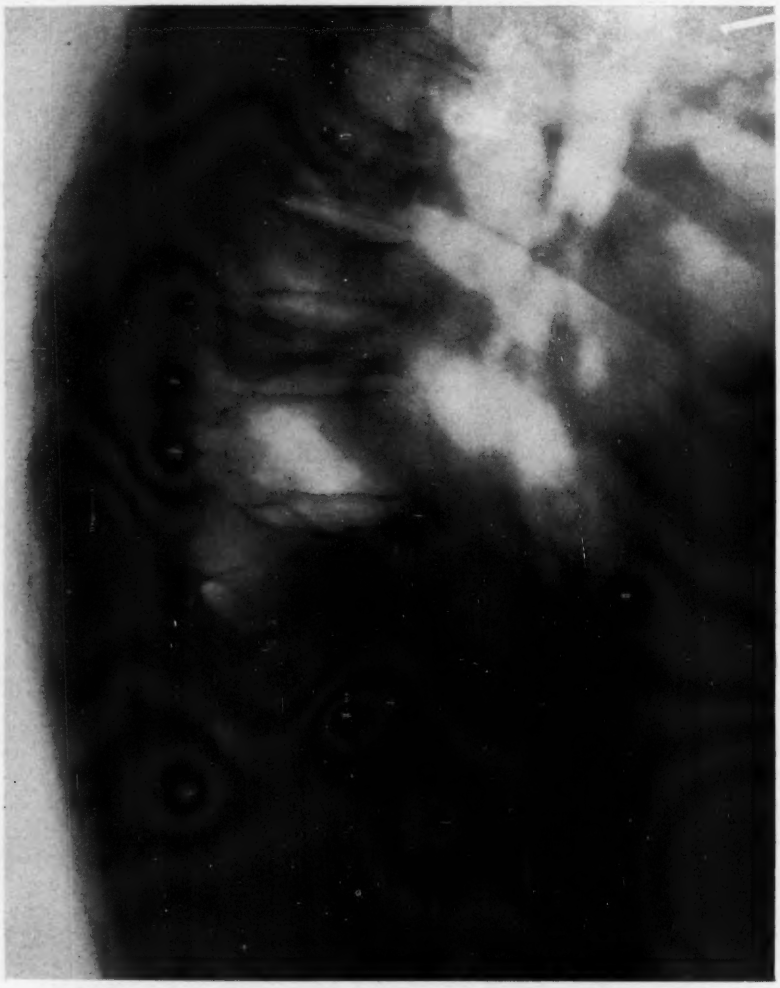

Fig. 9.—Roentgenogram of the same portion of the spine as in Fig. 9, but in lateral view.

Bence-Jones reaction of the urine was negative; basal metabolic rates were minus 19 per cent and minus 21 per cent. Kahn reaction was negative. The blood cholesterol was slightly elevated at 210 mg. per cent. The serum calcium was 9.9 mg. per cent and the serum phosphorus 3.5 mg. per cent. The serum phosphatase was slightly elevated at 8.8 Bodansky units. The patient improved with orthopedic management of the back and the administration of whole thyroid substance. He was last seen in Sept., 1939, when he was permitted to discard his brace.

That group of hypothyroid cases in which epiphyseal manifestations are noted mainly at the hip joints is very important because of the difficulty in differentiation from Legg-Calvé-Perthes disease.

Läwen in 1909 made the first clinical report of Legg-Calvé-Perthes disease in a cretin. Since 1920, when Engelbach designated the X-ray as a diagnostic factor in hypothyroidism, more cases of juvenile chondroepiphysitis or hypothyroid stippled epiphyses have appeared in the literature. That hypothyroidism bore a significant pathogenic relationship to stippled epiphyses was ably attested by the studies of Schaefer, Strickroot, and Purcell[17] in 1939. Two hundred fifty-eight endocrinopathic children from 8 to 15 years of age and ninety-nine

Fig. 10.—Patient N. S. Roentgenogram of the pelvis showing bilateral stippled epiphysis.

normal children in the same age group were subjects. In the former group, evidence of chondroepiphyseal disturbance was demonstrated in 35.2 per cent of the patients. Among these, all but six cases were definitely associated with hypothyroidism, and only two cases were symptomatic. In the control group only 7 per cent showed chondroepiphysitis. Follow-up has shown eight cases among the endocrinopathic group with a return to normal bone detail after thyroid treatment.

The pathologic changes[16] underlying this disease are of the greatest import if one is to understand fully the differentiating features from Legg-Calvé-Perthes disease. Two important changes are to be noted, one at the epiphyseal plate and the other in the epiphysis itself. In the former a layer of bone is formed consisting of bony trabeculae lying transverse to the long axis of bone. This layer was found by Langhans to be detectable not only histologically but also roentgenographically since it had sufficient density.[16] In the epiphysis there exists

Fig. 11.—Photograph of patient N. S.

from the earliest growth period a number of centers of bone growth or ossification which never coalesce and which are separated by an irregular abnormal type of cartilaginous structure. This is in direct contrast to the Legg-Calvé-Perthes epiphysis which prior to its diseased state consisted of an epiphysis with a single center of ossification from which normal bone growth advanced outwardly. When seen in the

later stages of both endocrine juvenile chondroepiphysitis and Legg-Calvé-Perthes disease, both epiphyses appear the same, since in the former necrosis has supervened on the abnormal cartilaginous structure, while in the latter multiple areas of aseptic necrosis are the feature of the pathology. In Legg-Calvé-Perthes disease the changes at the epiphyseal plate are not to be found.

With the above pathologic features well understood it is easier to consider the differential diagnosis. Hip involvement in hypothyroid stippled epiphysis is usually bilateral but unilateral in Legg-Calvé-Perthes disease. The presence of roentgenographic abnormalities in bones other than those about the hip, such as the knee and ankle, stamp

Fig. 12.—Patient N. S. Roentgenogram of the knees, with arrows indicating supracondylar osteoporotic bands.

the disease as endocrine in nature. No evidence of a destructive process is found in hypothyroid stippled epiphysis as is the case with Legg-Calvé-Perthes disease, although this feature is very often difficult to distinguish. Response to thyroid therapy is found usually in the endocrine group, whereas in Legg-Calvé-Perthes disease there is no such response. The following case report is one which illustrates the above features in great detail.

CASE 5 (Hosp. No. 82738).—N. S., a white male, aged 14 years, was admitted to the Hospital for Joint Diseases on Oct. 17, 1939, because of a left-sided limp which had been present for 2½ years. X-rays revealed bilateral stippled epiphysis (Fig. 10) and the diagnosis of Legg-Calve-Perthes disease was made. However, further study cast doubt on the diagnosis. A photograph of the patient resembled an individual of the hypothyroid-pituitary type (Fig. 11). Roentgenographs showed transverse supracondylar osteoporotic bands at the knee and ankle joints (Fig. 12). Other radiographic findings were slight thinning of the frontal bones, somewhat rudimentary and undeveloped sella turcica, and slight diminution in the vertical development of the long bones with increase in the widths of the shafts of the humeri.

Fig. 13.—Patient N. S. Roentgenogram nine months after the inception of treatment. Slight improvement in epiphyses to be noted.

The basal metabolic rate was minus 2 per cent. Treatment was instituted. Both hips were immobilized and thyroid substitution therapy begun. In five months the patient had lost more than twenty pounds. Marked improvement of the epiphyses is to be noted progressively on roentgenograms taken in July, 1940 (Fig. 13), and Jan., 1941 (Fig. 14). The patient is still under treatment.

HYPERTHYROIDISM

The changes taking place in the osseous system as a result of hyperthyroidism are of a different type from those discussed above. The first case recognized roentgenographically was by Kummer in 1917.

In 1938 Bartels and Haggart[2] of the Lahey clinic reported two cases with compression fractures of the vertebrae, in both of whom clinical improvement was obtained after surgical treatment of the hyperthyroidism.

The skeletal manifestation of the disease is that of osteoporosis and any of its attending complications. The osteoporosis is generalized but appears earliest in the small flat bones and the spine and in the long bones latest. In 1929 Aub and his co-workers[1] demonstrated that the loss of calcium from bone was associated with a negative calcium metabolic balance. It has been shown[1] that whereas normal persons excrete 12.7 Gm. of calcium per kilogram of body weight over a three-day

Fig. 14.—Patient N. S. Roentgenogram fifteen months after inception of treatment. Marked improvement to be noted in epiphyses.

test period, patients with thyrotoxicosis eliminate 42 Gm. per kilogram of body weight. With the increase of calcium excretion phosphorus also shows a negative balance. When thyrotoxic patients manifesting calcium hyperexcretion were fed iodine, the calcium excretion returned to normal. The serum calcium and phosphorus remain normal. Increase in the serum phosphatase values was demonstrated by Hunter[9] but these values were only moderately high.

The negative calcium balance has no relationship to increase in basal metabolic rate, since comparable increases in metabolism occur in high fevers and leucemia without the concomitant excretion of large amounts

of calcium. The calcium excretion was shown[1] to be dependent upon three principal factors: (1) the duration of the disease, (2) the rate of calcium loss, and (3) the daily calcium intake. As to the etiology of the disease, it is the general consensus of opinion that the thyroid secretions play some part directly on the calcium deposits of bone. Moehlig and Adler[14] proposed the theory of an alteration in glycogen metabolism secondary to changes in the pituitary gland.

Fig. 15.—Patient J. I. Roentgenogram of the knee joints, marked osteoporosis to be noted.

It is interesting to note that in most of the cases reported, the disease was of five or more years' duration. In the two cases reported by Bartels and Haggart[2] the total duration was nine years in one case and seventeen years in the other case before bone changes were noted clinically. In the case herein presented there was a five-year history. It is therefore not surprising that in cases of hyperthyroidism of less than five years' duration no evidence of osteoporosis is demonstrable.

Little is reported on the results of surgical therapy in regard to the skeletal changes. In the first case of Bartels and Haggart[2] no bone recalcification was found one year after operation. In a case reported by Moehlig and Adler,[14] decalcification of vertebrae and pelvis pro-

gressed in spite of thyroidectomy. Means and co-workers[13] presented a patient with improvement of kyphosis and flaring of the ribs following thyroidectomy. Our patient disclosed roentgenographic improvement eight months following surgery.

The following case report illustrates the above facts. Calcium excretion determinations were not obtainable.

CASE 6 (Hosp. No. 79405).—J. I., a male negro 12 years of age, was admitted to the Pediatric Service Oct. 9, 1939, and later transferred to the Surgical service. For four years the patient had noticed an increased "popping" of his eyes. Nervousness, polyphagia, excessive perspiration, and loss of ten pounds in weight were noted during the year prior to this admission. The thyroid gland was symmetrically enlarged and soft; a bruit was heard on auscultation. The skin was warm and moist. Eye signs were: marked exophthalmos, lid lag, and widened palpebral fissures. There was a fine tremor of the tongue and hands. The pulse was forceful and its rate ranged in the vicinity of 140. The liver was moderately enlarged.

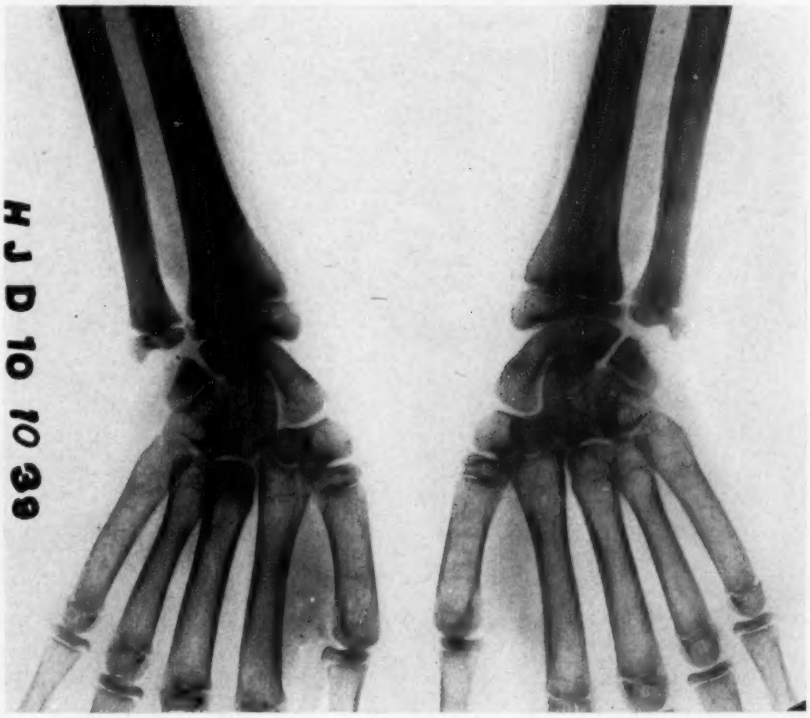

Fig. 16.—Patient J. I. Roentgenogram of both hands. Marked osteoporosis of the phalanges and carpus to be noted.

Basal metabolic rate was plus 29 per cent. The serum calcium and phosphorus were within normal limits, being 10 mg. per cent and 5.3 mg per cent respectively. Both the cholesterol and cholesterol esters were diminished, 146 mg. per cent and 103 mg. per cent respectively. The serum phosphatase was moderately elevated at 6.9 Bodansky units.

X-ray examinations of the skeleton revealed moderate atrophy or decalcification of the bones of the knee joint (Fig. 15), the bones of the carpus and the hand (Fig. 16), the bones of the skull (Fig. 17), and the osseous structures of the

shoulder joint. It is interesting to note that in this patient the areas of decreased calcification were most marked where the bone had been formed most recently, namely at the epiphyseal areas.

The patient was prepared with iodine therapy, during which time he gained ten pounds. A two-stage subtotal thyroidectomy was performed, with an eighteen-day interval between the stages. Pathology demonstrated hyperplastic thyroid with colloid involution. The postoperative course was uneventful and the patient made a good recovery. To date, follow-up in the outpatient department has shown no recurrence. The basal metabolic rate fifteen months following operation was plus 2 per cent. X-rays of the bones of the hands and the knees show a moderate degree of recalcification (Figs. 18 and 19).

Fig. 17.—Patient J. I. Roentgenogram of the skull, fairly marked degree of osteoporosis.

Another case, a female past the age of 50 years, was observed by one of us (M. B.). She sustained a fracture of the upper third of the humerus. The only history of trauma was a slight pull of the muscles. It was noted, however, that the patient had an exophthalmos which she stated had been present for about twenty years. There was no neck tumor. In addition to the fracture, radiographs disclosed osteoporosis of the long bones, the skull, and some segments of the spine. This was considered to be a case of "burned out" hyperthyroidism with osteoporosis.

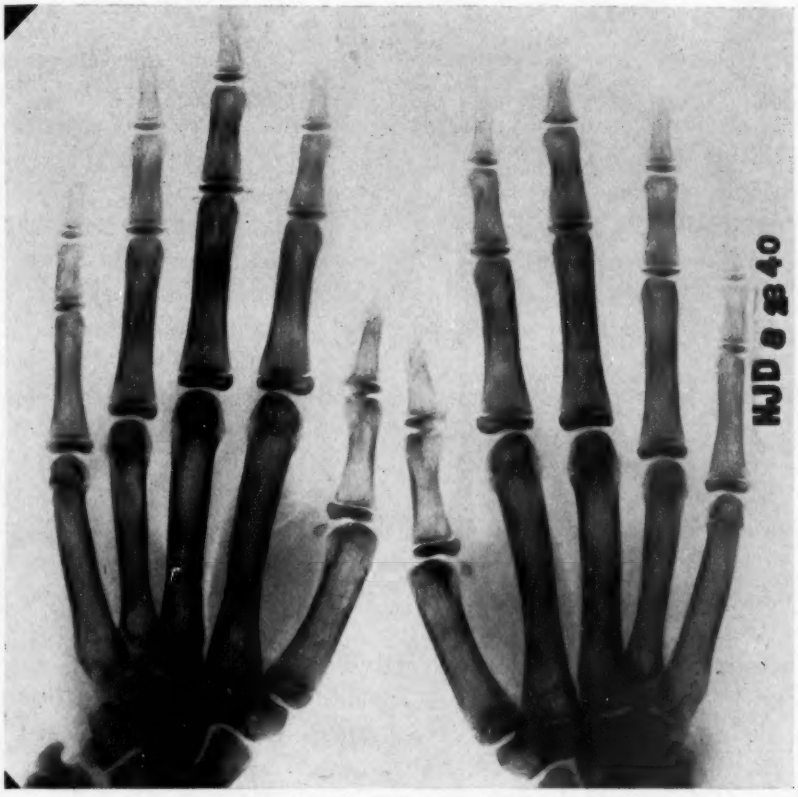

Fig. 18.—Patient J. I. Roentgenogram of the hands fifteen months after operation, showing considerable recalcification of the bones.

Fig. 19.—Patient J. I. Roentgenogram of the knee fifteen months after operation, showing recalcification.

SUMMARY AND CONCLUSIONS

From the discussions above it can be realized that not infrequently a bone lesion is diagnosed without the relationship of thyroid disease having been recognized. Pulsating tumors may be diagnosed as aneurysm, hemangioma, meningocele, or some other highly vascular tumor. The lesions are sometimes found on histologic examination to be secondary metastatic thyroid deposits occurring many years after the discovery of the primary lesion or even in the absence of any evidence of a primary lesion. Then again, the question of thyroid deposits in bone ever having been a metastasis or an aberrancy is still open. Bony lesions of thyroid origin also have simulated hyperparathyroid lesions, endothelioma, or multiple myeloma. Closer study reveals a differentiation.

Of all the skeletal manifestations of hypothyroidism perhaps the one most often unrecognized is stippled epiphyses of hypothyroidism. The characteristic pathologic changes of deficiency in centers of ossification, with irregularity of bone growth in addition to other characteristic changes at the epiphyseal plate, serve to differentiate this condition from Legg-Calvé-Perthes disease.

The osteoporotic changes of hyperthyroidism due to negative calcium balance are of great importance. Spontaneous fractures or fractures with little exciting cause have been reported in decalcified bones of a long-standing hyperthyroidism.

With thorough knowledge and understanding of the bone lesions described, treatment may be attempted on a more rational basis. Needling of so-called aneurysms of the spine will be attempted less often when one realizes that these lesions are often due to a thyroid metastasis. Thyroid substitution therapy in cases of stippled epiphyses is a great aid when definite evidence of hypothyroidism is established. Osteoporosis due to hyperthyroidism is sometimes benefited by thyroidectomy.

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THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST IN THE JAUNDICED PATIENT

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THE importance of a determination which might differentiate between obstructive jaundice and jaundice caused by destructive processes in the liver has been emphasized by Hanger:[1] "Patients with grave hepatitis are often subjected to the added hazard of an anesthetic and laparotomy to rule out possible biliary tract obstruction, while conversely, operation may be delayed perilously long in cases of obstruction in the hope that the jaundice will subside spontaneously." The differentiation clinically between these two types of jaundice is "frequently impossible despite careful history taking and physical examination, and the employment of many types of diagnostic procedure."

Hanger has recently demonstrated[1, 2, 4] that emulsions of sheep brain cephalin and cholesterol are regularly flocculated by sera of jaundiced patients with hepatocellular damage. Since such flocculation was not obtained with sera of normal individuals and patients with uncomplicated obstruction of the biliary tract, this simple test should prove of importance in the differential diagnosis of jaundice. Pohle and Stewart[3] attempted to evaluate the cephalin flocculation test in the light of various liver function tests, and were unable to confirm all of Hanger's findings. Most significantly, they found that nearly 80 per cent of cases of obstructive jaundice gave positive flocculation tests. Their data indicate that the cephalin flocculation test is of little or no value in the differential diagnosis of the two types of jaundice. Certain facts concerning the cephalin flocculation test, however, are agreed upon; viz., that (1) the test is negative in normal individuals, (2) it is only rarely if ever positive in patients without hepatic disease, (3) it is a more sensitive indicator of active liver parenchymatous disturbance than any of the so-called liver function tests, and (4) it provides the best available indicator as to prognosis in hepatic disease, especially in cirrhosis.[4] The purpose of this paper is to report our findings in jaundiced patients for the sole intent of evaluating the cephalin flocculation determination as a method of differentiating hepatocellular and obstructive jaundice.

METHODS AND MATERIALS

Sheep brain cephalin was obtained by dehydration of sheep brain with three extractions of acetone and three extractions with peroxide-free ether. The concentrated ether extracts were then precipitated

Received for publication, Oct. 4, 1941.

with four volumes of absolute alcohol and the resulting precipitate was taken up in minimum amounts of either. Cerebroside impurities were removed by chilling and centrifugation. The ether solution was reprecipitated with four volumes of absolute alcohol and the precipitate filtered, washed with alcohol and acetone, and desiccated. The stock solution was prepared by dissolving 100 mg. of sheep brain cephalin and 300 mg. of cholesterol in 8 c.c. of ether. The testing emulsion was prepared by adding 1 c.c. stock ether solution to 35 c.c. freshly distilled water, warmed to 65° C. and then heated slowly to boiling. The mixture was allowed to simmer until the final volume was reduced to 30 c.c., a process which disperses all coarse granular clumps and removes all traces of ether. The emulsion was then cooled to room temperature and 1 c.c. of the emulsion added to 0.2 c.c. of the patient's serum diluted with 4 c.c. of physiologic saline solution. The test tubes were allowed to stand at room temperature and were observed at the end of twenty-four and forty-eight hours as to the amount of flocculation and precipitation that had taken place.

A four-plus flocculation is indicated by complete precipitation, leaving the supernatant liquid water clear. Gradations of reaction between four-plus and negative may be found. As a general rule the reaction occurred within a few hours, with sera showing three-plus or four-plus flocculations, whereas one-plus and two-plus reactions might be observed at the end of twenty-four to forty-eight hours. No specimen was regarded as negative until forty-eight hours had elapsed without flocculation. The importance of avoiding such contaminants as anticoagulants, heavy metals, and strong acids has been emphasized by Hanger.[1]

In our first trials with the cephalin flocculation test we desired to control our method of preparation by testing with normal sera which should have shown negative reactions. However, we soon found that varying degrees of flocculation could be obtained, even four-plus reactions, in a most unpredictable manner. Communication with Dr. Hanger resulted in our receiving a preparation of cephalin which he had used in his observations. This preparation was darker in color and more gummy than those we had used, and gave reactions with normal sera which were entirely negative. The differences in flocculation are apparently dependant upon differences in "aging" and oxidation of the cephalin. Accordingly, in all subsequent observations we used Dr. Hanger's preparation and a preparation obtained from the Difco Company,* which we assayed and found to have approximately the same sensitivity. It was immediately apparent, however, that preparations of cephalin might vary in sensitivity depending upon slight variations in the preparation procedure and the "age" of the preparation. Rosenberg[5] has recently observed differences in the reaction obtained with

*We wish to thank Dr. C. W. Christensen of the Difco Laboratories of Detroit, Mich., for a generous supply of cephalin.

TABLE I

CASES OF JAUNDICE CAUSED BY OBSTRUCTION OF EXTRAHEPATIC BILIARY DUCTS

CASE NO.	INITIALS	SEX	AGE	DIAGNOSIS	BASIS FOR DIAGNOSIS	FLOCCULATION	ICTERUS INDEX	REMARKS
1	L.M.	M	73	Common duct stone	Operative	0	80	Test 1 plus when repeated
2	E.B.	F	30	Common duct stone	Operative	+	60	Reaction 2 plus after operation
3	M.T.	F	83	Common duct stone	Clinical	0	100	
4	M.H.	F	64	Common duct stone	Autopsy	0	75	Died after craniotomy
5	H.L.	F	50	Common duct stone	Operative	+	50	Negative flocculation 2 days later
6	M.P.	F	50	Common duct stone	Operative	++	60	Septicemia; died eighth postoperative day
7	C.N.R.	F	64	Common duct stone	Operative	0	45	Adenocarcinoma of ovary; metastasis to gall bladder
8	A.H.	F	61	Stricture of common bile duct	Operative	0	120	Associated cholecystitis
9	L.D.	F	40	Stricture of common bile duct	Operative	+	70	Died ninth postoperative day
10	B.P.	M	3 mo.	Congenital obliteration of bile ducts	Autopsy	+	60	Bile peritonitis
11	E.P.	M	58	Carcinoma of stomach	Operative	0	115	Complicating bronchopneumonia
12	B.R.	F	53	Carcinoma of pancreas	Clinical	0	100	Metastasis to liver and bile duct
13	B.D.	M	56	Carcinoma of pancreas	Operative	0	170	Patient left before operation
14	W.C.	M	76	Carcinoma of pancreas	Clinical	0	100	Obstruction common bile duct
15	V.D.	F	54	Carcinoma of pancreas	Operative	0	30	Obstruction common bile duct
16	J.H.	M	54	Carcinoma of pancreas	Operative	0	200	Obstruction common bile duct
17	S.W.	M	34	Carcinoma of pancreas	Clinical	0	35	Obstruction common bile duct
18	R.T.	M	60	Carcinoma of pancreas	Operative	+	100	Deserted
19	T.G.	M	41	Carcinoma of ampulla of Vater	Operative	+	125	
20	S.C.	M	60	Carcinoma of pancreas	Autopsy	+	50	
21	G.J.	F	29	Cholelithiasis	Operative	0	80	Syphilis; chronic cholecystitis
22	M.H.	F	46	Cholelithiasis	Clinical	0	60	Syphilis; chronic cholecystitis
23	M.M.	F	23	Cholelithiasis	Operative	0	100	Chronic cholecystitis
24	A.T.	M	48	Cholelithiasis	Clinical	0	12	
25	A.L.	M	57	Cholelithiasis	Operative	0	30	Chronic cholecystitis
26	J.H.	F	36	Cholelithiasis	Operative	0	50	Chronic cholecystitis
27	L.N.	F	49	Cholelithiasis	Clinical	0	50	X-ray diagnosis
28	P.F.	M	65	Cholelithiasis	Operative	0	50	

various cephalin preparations and suggested that cephalin be exposed to the air for a number of weeks to convert it to the "oxidized" form in order that false positive reactions may be avoided. Emulsions were freshly prepared on the day the tests were to be performed and a "normal" serum, to check suspension stability, was used as a control. The sera were obtained from jaundiced patients in Touro Infirmary and New Orleans Charity Hospital.* The sera of 50 jaundiced patients were studied.

The cases are divided into (1) cases of jaundice caused by obstruction of the extrahepatic biliary tract, and (2) cases of jaundice with hepatitis, but without demonstrable obstruction of the extrahepatic biliary tract.

1. *Cases of Jaundice Caused by Obstruction of Extrahepatid Biliary Tract.*—This group of 28 cases included practically all of the common types of obstructive processes involving the extrahepatic biliary tract; viz., stone in common bile duct, acute cholecystitis and cholelithiasis, stenosis of the common bile duct, congenital obliteration of the bile ducts, metastatic carcinoma of the liver and biliary tract, carcinoma of the head of the pancreas. From Table I, it is apparent that of the 28 cases, 20 showed negative flocculations, 7 gave a one-plus reaction, and 1 gave a two-plus reaction. The latter was complicated by septicemia. The 7 faintly positive reactions may have been caused by a low-grade hepatocellular damage associated with obstruction. Significantly no reaction stronger than a two-plus reaction was obtained. Two cases of obstructive jaundice showing three-plus reactions were omitted from Table II. One of these was diagnosed clinically as obstructive jaundice. The icteric index was 35 and the flocculation three-plus. One week later the flocculation was negative. The patient was operated upon the following day and cholecystgastrostomy performed. The head of the pancreas was indurated and the regional nodes enlarged. No malignancy was demonstrated. The final diagnosis was hepatitis and pancreatitis. It is doubtful that this case was one of extrahepatic obstruction. The second case had carcinoma of the head of the pancreas with a tremendously enlarged liver which extended 13 cm. below the costal margin. No liver sections were available. This case was obviously one of marked hepatitis complicating the picture of obstruction. On the basis of the above data, it seems reasonable to conclude that in obstructive jaundice the cephalin flocculation is predominantly negative or faintly positive.

2. *Cases of Jaundice With Hepatitis, But Without Demonstrable Obstruction of Extrahepatic Duct.*—These cases may be subdivided into two groups: (a) cases with acute catarrhal jaundice of unknown etiology, and undiagnosed hepatitis, and (b) cases caused by some chemical toxin. The first group comprises 12 cases with icteric indices

*We are indebted to Dr. William McCord of New Orleans Charity Hospital for collecting a number of sera from jaundiced patients.

TABLE II

CASES OF JAUNDICE WITH HEPATITIS BUT WITHOUT DEMONSTRABLE OBSTRUCTION OF EXTRAHEPATIC DUCT

CASE NO.	INITIALS	SEX	AGE	DIAGNOSIS	BASIS FOR DIAGNOSIS	FLOCCULATION	ICTERUS INDEX	REMARKS
1	C.R.	F	21	Acute catarrhal jaundice	Clinical	++++	100	Recovery
2	J.S.	M	5	Acute catarrhal jaundice	Clinical	+++	50	Recovery
3	M.S.	F	30	Acute catarrhal jaundice	Clinical	+++	150	Recovery
4	J.S.	M	49	Acute catarrhal jaundice	Clinical	++++	150	Recovery
5	I.D.	F	41	Acute catarrhal jaundice	Clinical	++++	75	Recovery
6	W.W.	M	50	Acute catarrhal jaundice	Clinical	++++	150	Recovery
7	A.C.	M	10	Acute catarrhal jaundice	Clinical	++++	85	Recovery
8	J.C.	M	40	Acute catarrhal jaundice	Clinical	+++	100	Recovery
9	G.K.	M	58	Acute catarrhal jaundice	Clinical	++++	120	Recovery
10	C.J.	F	19	Acute catarrhal jaundice	Clinical	+++	85	Recovery
11	F.H.	M	58	Acute hepatitis	Clinical	++++	200	Recovery
12	A.D.	M	50	Acute hepatitis	Clinical	++++	400	Complications: bronchopneumonia, Type I pneumococcal bacteremia; died
13	J.R.	F	54	Acute alcoholism	Clinical	+	30	Recovery
14	T.G.	F	33	Toxic hepatitis	Clinical	+++	70	Lysol burns of mouth, stomach, etc.
15	L.H.	F	25	Sulfathiazole hepatitis	Clinical	0	50	Pyelitis of pregnancy
16	V.W.	M	18	Arsphenamine hepatitis	Clinical	++++	32	Five-day mapharsen drip
17	D.J.	M	46	Arsphenamine hepatitis	Clinical	0	65	Recovery
18	L.H.	M	25	Arsphenamine hepatitis	Clinical	0	90	Recovery
19	B.G.	F	35	Arsphenamine hepatitis	Clinical	0	80	Recovery
20	L.H.	F	17	Arsphenamine hepatitis	Clinical	0	125	Recovery

as high as 400. In this group, three- and four-plus reactions were the rule. All patients except the one in Case 12 made an uneventful clinical recovery. Case 12 had a Type 1 pneumococcal bacteremia, bronchial pneumonia, syphilis, and a possible amoebic hepatitis.

The second group comprises cases of jaundice associated with some obvious poison including alcohol, sulfathiazole, and arsphenamine. In our small series the reactions obtained with these drugs are not predictable and are not particularly cogent from the diagnostic standpoint, for the etiologic factor responsible for the jaundice is apparent. Our results with arsphenamine are similar to those obtained by Hanger.[1] Recently Hanger and Patek[4] have published an extensive series of cases of cirrhosis of the liver in which the reaction may vary from a four-plus to a negative, depending upon the clinical status of the patient. The diagnostic and prognostic significance of their findings has been discussed by them. In cases with three- and four-plus reactions the speed with which the positive flocculation reaction appeared in the test tube was noticeably shorter than time reactions for one- and two-plus flocculation reactions.

DISCUSSION

In this series of cases of jaundice, our findings tend to confirm the observations of Hanger. Cases of jaundice caused by obstruction in the extrahepatic ducts give either negative or faintly positive reactions with the cephalin flocculation test. Rosenberg[5] has recently obtained similar results in 11 cases of obstructive jaundice proved by operation. Cases of jaundice associated with acute hepatitis give strongly positive reactions. In addition, we have noted that cases of jaundice associated with some obvious chemical poison may give unpredictable reactions. The data indicate clearly that there is a definite diagnostic significance to the cephalin flocculation test in the differential diagnosis of these two types of jaundice. Diametrically opposite conclusions were reached by Pohle and Stewart.[3]

While the duration and completeness of obstruction may be predominating factors in determining the amount of associated hepatitis, the data on the patients observed by Pohle and Stewart, Hanger, and ourselves are too different to be reconciled on the basis of differences in the degree of associated hepatitis. A more likely explanation would seem to be that Pohle and Stewart used a preparation which was more sensitive than the ones used by Hanger and ourselves. Indeed, Hanger has suggested that this may be the case.[4] We incline toward a similar view, even though Pohle and Stewart used a preparation less sensitive than our original preparations, in that they demonstrated negative flocculation reactions with normal sera. It would seem important that a single source supply of emulsion material should be used if accumulated data are to have comparative value. The cephalin-cholesterol material supplied to us by Difco Company seems trustworthy and is

being assayed in our laboratory at the present time. There seems to be some indication that it will soon be available on the market.

SUMMARY

The cephalin flocculation test was done on sera obtained from 50 jaundiced patients. A definite difference in flocculation reaction was observed in cases of jaundice caused by obstruction of the extrahepatic biliary tract and in cases of jaundice with hepatitis, but without demonstrable obstruction of the extrahepatic duct. On the basis of our data it seems justifiable to conclude that the cephalin flocculation reaction is of diagnostic value in the differential diagnosis of obstructive jaundice and jaundice caused by hepatitis. The importance of the use of a uniform preparation, obtained from a single large standardized batch, in a larger series of cases has been emphasized. It is recommended that the test be applied to the sera of all jaundiced patients.

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AN EVALUATION OF INTESTINAL SUCTION IN INTESTINAL OBSTRUCTION

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INTESTINAL suction was introduced for the treatment of intestinal obstruction almost four years ago.[1] Enough data are now available so that statistical evaluation of this therapy is possible.

SELECTION OF CASES

The cases used in this analysis are derived from a study of all cases of intestinal obstruction treated at the Peter Bent Brigham Hospital from 1933 to July, 1941. To these have been added all available cases from the American literature that satisfy the requirements of the classification.

When the influence of any one factor on a series of cases is to be studied, the test series should be as similar as possible to the control series except in respect to the factor under consideration. The control series in this study is therefore comprised of cases treated since Wangensteen[2, 3] established duodenal suction as an accepted therapy in obstruction. Prior to this it had been recognized that control of the fluid and electrolyte balance was essential in the treatment of intestinal obstruction. The test series consists only of cases in which the Miller-Abbott tube, or other long tube, had definitely passed into the jejunum.

In order to compare similar types of intestinal obstruction, two distinct groups were chosen for analysis: (1) simple mechanical obstruction of the small or large bowel; (2) intestinal obstruction associated with peritonitis. It will be seen that the mortality of these two groups is so different that they must be considered separately in evaluating any therapy applied to them.

"Paralytic ileus" not associated with peritonitis is too poorly defined a clinical entity to constitute a definite group for an analysis of this sort, although individual cases may yield satisfactorily to intestinal suction.

STATISTICAL METHOD

Obviously, no statistical significance can be attached to the difference in percentages of two series unless the difference is considerably greater than that which might occur through chance. The range of the probable variation of the difference between percentages in two

Received for publication, Oct. 13, 1941.

series can be computed by a formula* and is known as the standard error of the difference.[4] The formula takes into account the total number of cases in each series and also the individual percentages to be compared. To be statistically significant, the difference between the percentages of two compared series must be at least 2.5 times the computed standard error of the difference. This fact may become clearer if stated in another manner. The probability that the difference between percentages of any two series is due to chance may be determined mathematically by comparing the difference with the computed standard error of the difference. If the difference between the percentages is 2.5 times their standard error, the odds are 80 to 1 that the difference did not occur by chance; if the difference is 3 times their standard error, the odds are at least 369 to 1 against the difference being due to chance.

SIMPLE MECHANICAL INTESTINAL OBSTRUCTION

Fifty-six cases of mechanical intestinal obstruction were treated without intestinal suction at the Peter Bent Brigham Hospital between 1933 and 1941. Table I summarizes the mortality figures of these cases and

TABLE I

MECHANICAL INTESTINAL OBSTRUCTION (INTESTINAL SUCTION NOT USED)

AUTHORS	CASES	DEATHS	
Van Buren and Smith[5]	78	15	
Scudder et al.[6]	14	3	
Wangensteen et al.[7]	116	13	
Glenn[9]	42	14	
Peter Bent Brigham Hospital	56	8*	
	306	53	(17.3% mortality)

*Five cases failed to improve with gastric or duodenal suction. Seven cases had obstruction due to malignancy. All but 2 patients, who were essentially moribund, had complications contributing to their death: 2 patients died of circulatory failure (1 due to heart failure, the other due to shock); 2 cases were complicated by pneumonia and 2 by pulmonary emboli.

of the cases of mechanical intestinal obstruction appearing in the American literature between the time that duodenal suction was generally used and intestinal suction was introduced. This is a control series of 306 cases with a mortality of 17.3 per cent.

Table II gives the cases and deaths in mechanical intestinal obstruction treated with intestinal suction. The total number of cases is 151; the mortality is 7.9 per cent or essentially 8 per cent.

It appears, therefore, that when intestinal suction is added to the usual measures of treatment of mechanical intestinal obstruction, the mortality is reduced from 17.3 to 8 per cent. Since the difference between these percentages (9.3) is three times the standard error of the

* $\sqrt{\frac{\text{Percentage A} \times (100 - \text{Percentage A})}{\text{No. of Cases in Series A}} \text{ plus } \frac{\text{Percentage B} \times (100 - \text{Percentage B})}{\text{No. of Cases in Series B}}}$

difference (3.1), the reduction in the mortality due to the use of intestinal suction is of undeniable significance because the odds are 369 to 1 against this difference being the result of chance.

TABLE II

MECHANICAL INTESTINAL OBSTRUCTION (INTESTINAL SUCTION USED)

AUTHORS	CASES	DEATHS	
Abbott[10]	14	2	
Wise[11]	3	0	
Wangensteen et al.[7]	9	3	
Leigh et al.[12]	38	1	
Duncan[13]	3	0	
Willson[14]	22	0	
Bennett[15]	9	0	
Glenn[9]	34	5	
Peter Bent Brigham Hospital	19	1*	
	151	12	(7.9% mortality)

*This was a 42-year-old female who was given fair relief of symptoms of obstruction by intestinal suction but who died of multiple carcinomatosis.

INTESTINAL OBSTRUCTION COMPLICATED BY PERITONITIS

When peritonitis is associated with intestinal obstruction, the mortality is greatly increased. To evaluate the effect of intestinal suction on this condition, our cases have been added to all acceptable cases appearing in the literature. No distinction was made on the basis of the extent of peritoneal involvement. The cases treated without intestinal suction are listed in Table III and those treated with intestinal

TABLE III

OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION NOT USED)

AUTHORS	CASES	DEATHS	
Van Buren and Smith[5]	13	12	
Leigh et al.[12]	7	6	
Peter Bent Brigham Hospital	36	23*	
	56	41	(73.1% mortality)

*Causes of death: 17 patients failed to be improved by gastric or duodenal suction; 12 suffered from pulmonary complications which contributed to their death (7, atelectasis; 5, pneumonia).

The age distribution was 3 cases under 30 years; 11 cases, 30 to 59 years; the remainder, over 60 years.

suction appear in Table IV. The total number of cases in each group is not large, because authors seldom list their cases of obstruction and peritonitis separately and satisfactory intubation is difficult in the presence of peritonitis. However, the difference in mortality percentages of these groups is highly significant. The mortality in the control series of cases with obstruction and peritonitis that were not treated with intestinal suction is 73.1 per cent. But the mortality in the same type of case when treated with intestinal suction is 25 per cent. The difference between 73.1 and 25 per cent is 48, which is more than five times the standard error of the difference (8.2) and thus of undeniable statistical significance. The odds are greater than a million to one that the difference is not due to chance.

TABLE IV

OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION USED)

AUTHORS	CASES	DEATHS	
Abbott[10]	3	1	
Leigh et al.[12]	14	1	
Penberthy et al.[16]	6	2	
Duncan[13]	1	0	
Bennett[15]	4	4	
Glenn[9]	14	2	
Wangensteen et al.[7]	3	1	
Peter Bent Brigham Hospital	7	2*	
	52	13	(25% mortality)

*One patient was a 58-year-old female with generalized peritonitis due to acute appendicitis with perforation. Duodenal suction for eight days gave little improvement. Intestinal suction for seven days reduced x-ray evidence of distention but did not improve patient's condition. She died of overwhelming peritonitis of *Bacillus coli* and *Streptococcus faecalis* origin. The other patient was a 69-year-old male with generalized peritonitis due to acute appendicitis with perforation. Intestinal suction for eight days prevented x-ray evidence of distention. Patient died of peritonitis and toxic hepatitis.

TABLE V

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION (INTESTINAL SUCTION NOT USED) (1933-JULY, 1941)

ETIOLOGY OF OBSTRUCTION	NO. OF CASES	SITE OF OBSTRUCTION		OPERATION		DEATHS
		SMALL BOWEL	LARGE BOWEL	YES	NO	
Postoperative adhesions	28	28		24		1
					4	0
Gallstone	2	2		2		0
Impacted fecalith	1	1		1		0
Carcinoma	25	2		2		0
			23	22		6
					1	1

TABLE VI

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION (INTESTINAL SUCTION USED)

ETIOLOGY OF OBSTRUCTION	NO. OF CASES	SITE OF OBSTRUCTION		OPERATION		DEATHS
		SMALL BOWEL	LARGE BOWEL	YES	NO	
Postoperative adhesions	11	11		5		0
					6	0
Femoral hernia	1	1			1	0
Carcinoma	7	2		1		0
					1	1
			5	5		0

DISCUSSION

This evidence that the use of intestinal suction is an essential factor in reducing the mortality of intestinal obstruction parallels the experience of Johnston[18] and Leigh and his co-workers[12] in their own clinics.

TABLE VII

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF INTESTINAL OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION NOT USED)

ETIOLOGY OF PERITONITIS AND OBSTRUCTION	NO. OF CASES	OPERATION		DIED
		YES	NO	
Appendicitis	10	10		3
Perforations of gastrointestinal tract	7	5		2
			2	2
Inflammation of female internal genitals	3	3		1
Ulcerative colitis	1	1		1
Septic abortion	1	1		1
Prostatectomy postoperatively	1	1		1
Carcinoma of large bowel	10	9		8
			1	1
Lymphosarcoma of small bowel	2	2		2
Metastatic carcinoma of small bowel	1	1		1

TABLE VIII

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION USED)

ETIOLOGY	NO. OF CASES	OPERATION		DEATHS
		YES	NO	
Appendicitis	3	3		2
Perforation of large bowel	2	2		0
Inflammation of female internal genitals	1	1		0
Total hysterectomy postoperatively	1	1		0

Intestinal suction is an ideal physiologic treatment because it produces an outlet for the intestinal contents at a point just proximal to the obstruction. As the intestine is decompressed, the circulation is improved, the smooth muscle regains its normal tone, and the important function of nutrition may be resumed. When the pressure within the intestine is released, the volume of circulating plasma, which has been shown to be reduced in obstruction, is restored to normal. Reduction of the intra-abdominal pressure by the decompression of the intestine allows normal circulation in the great venous channels and normal diaphragmatic excursion. Preoperative decompression of the alimentary tract by intestinal suction may avoid the necessity of colostomy or enterostomy and presents the operator with undistended bowel of normal thickness and tone. Intestinal suction continued into the postoperative period protects the anastomosis by preventing intraluminal pressure which might "blowout" the suture line or impair its circulation.

Lest this evidence be considered as indicating the desirability of intestinal suction in all cases of obstruction, the contraindications should be emphasized. When a reasonable possibility of vascular strangulation exists, intestinal suction should not be resorted to except as preparation for immediate operation. The danger is that although decompression offers no relief for the vascular obstruction, it may mask the symptoms to such an extent as to minimize the urgency of operation which is the essential therapy for intestinal strangulation. The decision for immediate operation depends upon nice clinical judgment of all facts at hand. If strangulation cannot be ruled out, surgery should be advised. Willson[14] and others have pointed out that intestinal intubation should not be attempted in cases of obstruction of the large bowel which show great distention of the colon and little evidence of distention of the small bowel. The rationale of this suggestion is that under these circumstances, the ileocecal valve is still competent and does not permit the pressure within the large bowel to be relieved by regurgitation into the ileum. In such cases, the dangerous pressure on the colon cannot be reduced until the tip of the long tube has passed through the ileocecal valve. The passage of the tube through the whole small bowel may not be complete for days, and even then it may be impossible to get the tip to pass through the competent ileocecal valve. Accordingly, intestinal intubation is not the treatment of choice because the relief of pressure in the large bowel may be unwisely delayed.

The reduced mortality from the proper use of intestinal suction depends upon successful intestinal intubation and the maintenance of continuous suction. Intubation may be difficult or, rarely, impossible. During intubation and suction, both patient and apparatus require the closest supervision and attention to details. It is the universal experience of clinics using the technique extensively that the number of failures of intestinal suction is greatly reduced by increased knowledge of the details of technique and earlier decisions to employ intestinal suction.[18] Whipple[19] states: "The reason that so many hospitals have failed to appreciate the value of the Miller-Abbott tube in dealing with cases of ileus is that no one person has learned the application and technique of the method and acquired the experience necessary to its success." The details of the technique of the method have been published by those who devised the apparatus and others who have had clinical experience in its use.[10, 12, 17, 20] Whatever effort is involved in acquiring and applying the technique is certainly justified by the fact that intestinal suction is a life-saving procedure as an adjunct to the treatment of obstruction.

CONCLUSIONS

The use of intestinal suction in the treatment of intestinal obstruction has resulted in a statistically significant reduction in mortality.

The mortality in 306 cases of mechanical obstruction treated without intestinal suction is 17.3 per cent. In 151 cases of the same type treated with intestinal suction the mortality is 7.9 per cent.

The mortality in 56 cases of obstruction with associated peritonitis treated without intestinal suction is 73 per cent. But in 52 cases of the same condition treated with intestinal suction the mortality is 25 per cent.

The clinical value of intestinal suction in reducing the mortality of obstruction justifies the effort of acquiring and applying the technique.

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A STUDY ON THE MECHANISM OF ACTION OF PROSTIGMINE ON INTESTINAL MOTILITY IN THE HUMAN BEING AND IN THE DOG*

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ESERINE has been used by veterinarians to overcome distention and atony of the intestinal canal in animals. In recent years eserine has been employed for the same conditions in the human being and in two reports from this laboratory its effects on intestinal motility of normal dogs and of dogs with peritonitis have been demonstrated.[1, 2] Recently prostigmine, an eserine derivative, has been used widely due to its relative lack of the undesirable by-effects of eserine.

While many reports have been published on the effects of eserine[1, 2] and of prostigmine[3 et al.] on intestinal motility in the normal and in the diseased man and animal, we have been interested in another angle of this question; namely, whether under pathologic conditions such as peritonitis, inflammation or distention of the intestine, any or enough acetylcholine would be liberated at the parasympathetic nerve endings of the intestine to produce peristalsis. It has been shown recently that nervous impulses failed to be transmitted to the effector organs when vascular tone was low.[4] The effects of eserine or prostigmine in the usual doses administered to man are considered to be due to their inhibitory action on blood esterase, the ferment which hydrolyses acetylcholine after it has been formed at the nerve endings and has acted on the intestinal musculature. If under pathologic conditions, normal activity of the parasympathetics should be abolished, and if the effects of eserine or prostigmine would be only through stimulation of parasympathetic activity, we could not expect beneficial effects under these conditions. With these questions in mind tests were performed on patients with ileostomies, cecostomies, or colostomies, and on normal anesthetized dogs.

METHODS

The patients had taken nothing by mouth since the night preceding the test, which was performed in the morning. A rubber balloon was inserted into the fistula and connected to an oil carbon tetrachloride

*Aided by the Gusta M. Rothschild Fund.

†We are obliged to Dr. Alfred Strauss and Dr. Siegfried Strauss for the use of their patients.

Received for publication, Sept. 10, 1941.

manometer (specific gravity, 1.5), and intestinal motility was recorded on the kymograph. The fistulas had been installed for carcinoma of the intestine, ileitis, or colitis. At the time of the experiments the patients were in good condition. A control period of at least thirty minutes was taken to establish the prevailing rhythm of intestinal motility. After that each patient received an intramuscular injection of 1 mg. of prostigmine methylsulfate, and during another test performed one to two weeks later, 1 mg. of prostigmine* plus 50 gammas of acetylcholine. The record was continued for two to four hours following the injection.

In the animal experiments, normal dogs anesthetized with nembutal were employed. Blood pressure was recorded from the carotid artery and heparin was used as anticoagulant. Intestinal motility was recorded by balloons inserted in the jejunum, the ileum and the colon, using the same type of manometer as described above. All injections were given intravenously.

RESULTS

Fifteen human subjects with intestinal fistulas were used. The records of all fifteen patients used regularly showed stimulation of intestinal motility by prostigmine and prostigmine-acetylcholine. No difference was found, however, between the prostigmine and acetylcholine-prostigmine mixture. This may have been due to the small amount of acetylcholine employed. In previous experiments on animals with peritonitis, we have found that the combination of eserine and acetylcholine produced more intestinal motility than eserine alone.[2] We believe that in our present experiments, the acetylcholine was not destroyed by the blood esterase because it must have been adequately protected against this enzyme by the rather large amount of prostigmine injected with it. We did not wish, however, to take the risk of injecting larger amounts of acetylcholine in view of untoward reactions which we had experienced in previous work. In a number of patients intestinal motility was stimulated so strongly by prostigmine that the balloon was pushed out of the fistula and in some cases evacuation of fecal material occurred. A few patients experienced cramps which were not particularly strong or disturbing.

Meyer and Necheles[5] have reported tests on patients with megaesophagus in whom the injection of prostigmine was followed by increased tone and peristalsis of the esophagus, and in experiments on esophageal motility of the dog they have been able to show that prostigmine was still effective on the esophagus after atropinization of the animal; that is, that prostigmine had an effect not only through the parasympathetic nerves, but also directly on the musculature. The experiments on the dog reported here were therefore conducted with

*Supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

this experience in view. If the intestine reacted to prostigmine after atropinization, this purely muscular effect of prostigmine would give us the assurance that in a damaged intestine in which the parasympathetic stimuli could not be effective, we might still be able to produce motility with its beneficial effects such as evacuation of gas, fecal material, etc.

Fig. 1 represents a typical experiment on a dog. Following a suitable control period, the injection of 0.5 mg. of prostigmine intravenously was followed by a steep rise of tonus of the colon and defecation. Tonus and motility of the jejunum rose likewise, but not as markedly as that of the colon. Following this, 2 mg. of atropine was injected intravenously and was followed by a decrease of tone and of contractions of both jejunum and colon. Twenty-five minutes later, the intravenous injection of 0.5 mg. of prostigmine was followed by increase of tone and motility of the jejunum and slightly increased motility of the colon. When the same injection was repeated nine minutes later, both colon and jejunum responded with increased tone and motility. Twenty-eight minutes later, an additional dose of 2 mg. of atropine was injected intravenously in an attempt to obtain more complete atropinization. Nevertheless, 1 mg. of prostigmine still evoked motility and tone in jejunum and colon. After atropinization, the blood pressure depressing effect of prostigmine was abolished. A dose of 50 gammas of acetylcholine injected intravenously did not affect jejunal and colonic motility following the last injection of prostigmine.

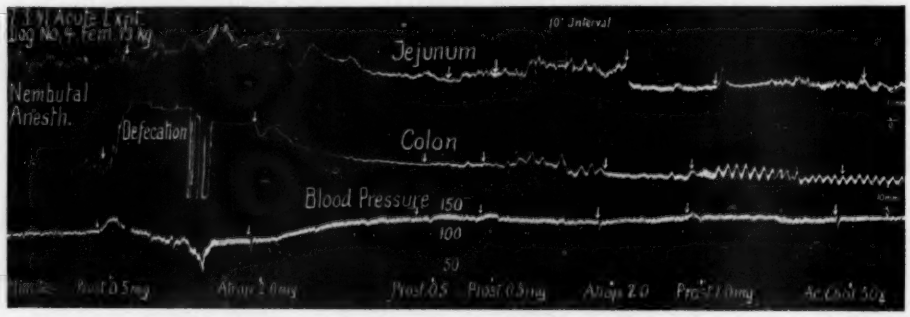

Fig. 1.—Intravenous injections: (1) prostigmine methylsulfate, 0.5 mg.; (2) atropine sulfate, 2.0 mg.; (3 and 4) prostigmine methylsulfate, 0.5 mg.; (5) atropine sulfate, 2.0 mg.; (6) prostigmine methylsulfate, 1.0 mg.; (7) acetylcholine HCl, 50 gammas.

DISCUSSION

In the experiments on the patients, we have found that a dose of 1 mg. of prostigmine was safe and without any serious or disagreeable by-effects, except slight cramps in a few patients, and that a combination of 1 mg. of prostigmine with 50 gammas of acetylcholine was not more effective in producing intestinal motility than 1 mg. of prostigmine by itself. We feel that the dose of acetylcholine may have been

too small, and that with a larger dose distinct effects would have been obtained, but we did not want to use higher doses in view of the dangers involved in such a combination of drugs, and in view of the relative weakness of our subjects. The experiments on the dog have given us valuable experience concerning the mechanism of prostigmine on the intestine, and we feel certain that this experience can be applied to the human being as well; namely, that the motor effect of prostigmine on the intestine is not only an indirect one through the endings of the parasympathetic nerves, but also a direct one on the musculature of the intestinal canal. Acetylcholine alone had no effect following a large dose of atropine. This was not the case when prostigmine was given; that is, its direct muscular effect had become evident. Prostigmine, therefore, produces intestinal motility not only by an indirect effect through the parasympathetic nerves, but also by a direct effect on the intestinal musculature, as we were able to show also for the esophagus.[5] We conclude, therefore, that when the parasympathetic nerves or their endings in the intestine have suffered following pathologic conditions, prostigmine may yet be expected to be effective due to its direct muscular effects, provided that the intestinal musculature is still viable. It is evident, however, that prostigmine or any similar drug should not be given in case of damaged intestine which may be expected to perforate.

SUMMARY AND CONCLUSIONS

The effect of intramuscular injection of 1 mg. of prostigmine to patients with ileal, cecal, or colonic fistulas has been tested. In every instance a good response of intestinal motility lasting from thirty to sixty minutes was found. A mixture of prostigmine and acetylcholine did not have any better effect than prostigmine alone. No serious or disturbing by-effects of the injection of prostigmine were observed. In experiments on dogs it was found that the effects of prostigmine on the intestinal musculature are twofold; namely, through stimulation of the parasympathetics and through direct stimulation of the intestinal musculature. Following atropinization of the animal, acetylcholine was not effective, while prostigmine still evoked distinct rhythmic motility and increased tone of jejunum and colon. We feel, therefore, that the administration of prostigmine to patients with intestinal paralysis, in whom the nervous motor mechanism may have suffered, is a good procedure. The weight of the patient should be considered in the computation of the dose of prostigmine. Patients below 125 pounds of body weight should receive proportionately less than 1 mg., which seems to be adequate for persons at or above that weight. In cases of impending perforation of the intestinal walls prostigmine should not be used.

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EXPERIMENTAL INVESTIGATION OF GASTROINTESTINAL SECRETIONS AND MOTILITY FOLLOWING BURNS AND THEIR RELATION TO ULCER*

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ALTHOUGH gastrointestinal ulcers following burns are not frequent, there is no doubt that their incidence has been higher than that of a normal population.[1] Many theories concerning the cause of Curling's ulcer have evolved during the last 100 years, but no systematic work on gastrointestinal secretions and motility following burns was found. Harkins reviewed the literature extensively in 1938 and found it to be rather contradictory.[1] A number of authors have held toxic substances to be responsible for the development of Curling's ulcer. These substances have been believed to be the product of the burn in the affected area and have been supposed to damage the gastric and duodenal mucosa either directly from the blood, or indirectly from the bile following their excretion in the liver, or still more indirectly by diminution of bile secretion through the toxic effects of such substances on the liver. Gastric hyperacidity following burns, acting on areas already damaged by burn toxins, were held responsible by Levin in 1929,[2] but Wilson in 1935[3] could not confirm this. Levin's assumption of hyperacidity[2] was not based on any experimental or factual evidence. Tinel and Ungar reported increased volume of gastric secretion following immersion of the foot of an anesthetized dog in water of 50° C. for two minutes.[4]

Our work was directed to observations on the effects of burns on gastrointestinal secretions and motility.

The literature on the effects of shock in general on the gastrointestinal mucosa of man has been reviewed recently by Harkins,[1] Penner and Bernheim,[5-7] and Klemperer and collaborators.[8] From a study of the literature and from our own experience we know that following shock from any kind of trauma, gastritis, duodenitis, or enteritis with petechiae, congestion, edema of the mucous membranes, and erosions or ulcers may be found.

Experimental Technique and Procedure.—Normal, healthy, fasting dogs (thirty hours) were anesthetized with pentobarbital sodium (nembutal) or with ether, and were kept under anesthesia for the entire duration of the experiment. Unless the animals died, they were destroyed rapidly and, needless to say, painlessly at the termination of the experiments. Blood pressure was recorded in the usual way from

*Aided by the A. B. Kuppenheimer Fund. A preliminary report was read at the Meeting of the Am. Physiol. Soc., Chicago, 1941.
Received for publication, Oct. 14, 1941.

the carotid artery with a mercury manometer. Respiration was recorded by a cuff placed round the chest; intra-abdominal pressure from a balloon placed between liver and diaphragm; and gastric, duodenal, and colonic motility by balloons placed in these organs. The various motilities were recorded by manometers filled with a mixture of oil and carbon tetrachloride, with a specific gravity of 1.5. Gastric secretion was collected either by suction from a tube tied in the pylorus, or by gravity from a cannula in the most dependent part of the stomach, the animal being placed on its abdomen on an operating table tilted upward at an angle of about 30°; in other experiments the esophagus was ligated in the neck and the pylorus just beyond the sphincter, and gastric secretions were collected at the termination of the experiment. Salivary secretion was collected from one submaxillary duct, biliary secretion from the common duct, with the cystic duct ligated, and pancreatic secretion from the main pancreatic duct. Each drop of these secretions was recorded by an instrument described by us.[9] The volume of gastric juice was marked on the kymograph record for every 10 c.c. of secretion collected. In one group of animals the unstimulated fasting secretions were collected. In another group secretions were stimulated at regular intervals during the control period and following trauma or burns.

More or less extensive torch burns were applied to the hindleg and the lower part of the back. In one experiment one hindleg was scalded.

A number of animals were used as controls to determine the effects of anesthesia alone. In order to check the degree of shock in the controls and in the shock series, circulating time,[11] plasma CO_2, hematocrit, hemoglobin and plasma proteins were determined in most experiments.

RESULTS

A. Secretions.—

1. Controls for Salivary, Pancreatic, and Biliary Secretion.—In 4 control experiments without burns constant injection of glucose (5 per cent)-saline (0.9 per cent) solution at the rate of 2 c.c. per minute was administered by a pump described previously.[10] Hourly intravenous injections of pilocarpine nitrate, 0.25 to 0.5 mg., or of secretin,* 5 to 10 mg., were given alternately, and in the following a change of secretion denotes changes in stimulated secretions.

In 3 of the control animals, in which salivary secretion was recorded, no change was noted. Two of these experiments lasted twelve hours and 1 lasted six hours. Of 3 control experiments, in which bile secretion was recorded, in 1 no change was noticed over a period of twelve hours and in the other 2 a slight decrease occurred in experiments lasting twelve and four hours respectively. In 3 experiments, in which pancreatic secretion was recorded, no change was noted in experiments lasting twelve, twelve, and four hours respectively. In all control animals

*Kindly supplied by Dr. D. Klein, of the Wilson Laboratories, Chicago, Ill.

blood pressure fell gradually as the experiments progressed, but the animals maintained a mean blood pressure of about 100 mm. during the greater part of the experiment.

2. Burns.—

(a) *Salivary, Pancreatic, and Biliary Secretion:* Control periods of several hours' duration preceded the burn. All animals received constant infusion of glucose-saline solution and alternating injections of pilocarpine and secretin, as described above, under "Controls." Experiment 1 lasted six and one-half hours; blood pressure fell gradually from 115 to 40; salivary secretion decreased 50 per cent. Biliary secretion was not affected by the first small burn on one leg, but decreased by 50 per cent following more extensive burns. Pancreatic secretion was diminished 50 per cent. The volume of gastric secretion rose considerably following the burn (Table I, Experiment 26). Dog 2, in an experiment lasting ten hours, showed salivary and gastric secretions (Table I, Experiment 27) considerably increased following a burn, while biliary secretion decreased 50 per cent. After a second and third more extensive burn, biliary secretion was inhibited 75 per cent and urinary secretion 50 per cent (collected from one cannulated ureter). In Dog 3, in which one hindleg was scalded, blood pressure gradually dropped from 150 to 40, and a 60 per cent decrease of salivary, biliary, and pancreatic secretions was noted. Gastric secretion rose considerably (Table I, Experiment 28). The experiment lasted six hours.

(b) *Gastric Secretion (Tables I and II):* In Experiments 4, 5, 13, and 23 to 29 esophagus and pylorus were ligated and gastric juice was collected from a cannula (v.s.). In the other experiments esophagus and pylorus were ligated and gastric contents measured at the termination of the experiment. A solution of 0.9 per cent NaCl with 5 per cent glucose was used when constant injection was given.

Tables I and II show that the resting stomach of 10 anesthetized animals secreted small amounts of fluid varying between 0 and 10 c.c. per hour (controls of Experiments 3 to 5, 11 to 13, and 17). Intravenous infusions of saline-glucose solution, starving* for thirty hours, feeding† ten hours before the experiments, and the injection of pilocarpine (Experiments 26 to 29) did not affect this secretion noticeably; its acidity was low, with no free acid and between 10 and 20 degrees of combined acid (i.e., cubic centimeters of N/10 HCl in 100 c.c. of gastric juice).

When animals were subjected to burns, those not receiving intravenous infusions did not show a significant change in gastric secretion. On the other hand, in the experiments in which intravenous infusion was administered, the quantity of gastric secretion rose considerably in volume in all animals, and in acidity in a number of them. Administration of food ten hours before the burn seemed to enhance the secretion of acid. In the experiments in which drugs were employed (Experiments 23

*All animals had access to water.
†Meat, cereals, bread, and vegetables.

TABLE I

GASTRIC SECRETION FOLLOWING BURNS

EXPERIMENT NO.	INTRAVENOUS		GASTRIC SECRETION					GASTROINTESTINAL PATHOLOGY (AND REMARKS)
			CONTROL		AFTER BURN			
	INFUSION C.C. PER MIN.	INJECTIONS DRUGS	HR.	C.C. PER HR.	TIME PERIOD	VOLUME C.C.	C.C. PER HR.	
Starving; no infusion; burn								
1					6 hr.	22	3.7	Slight duodenitis
2					6 hr.	80	13.3	Many worms; jejunum and ileum hemorrhagic where worms were found; dog sick with beginning distemper (?)
Starving; infusion; no burn								
3	17		4½	2.7				None
Starving; infusion; burn								
4	5		3½	2.9	First burn 30 min.	11	22.0	Gastritis and edema
					120 min.	2	1.0	
					45 min.	10	12.5	
					35 min.	10	17.0	
					40 min.	5	7.5	
					Second burn 75 min.	10	8.0	
					45 min.	10	13.3	
5	3		3	10.0	9 hr.	33 233 (acid)	30.0	Gastritis and prepyloric ulcer (acidity 74/85)
6	5				4 hr.	20	5.0	Edema
7	5				4 hr.	175 (acid)	44.0	Edema (acidity 120/126)
8	17				4 hr.	75	19.0	Edema
9	6				6 hr.	48	8.0	Food in stomach; edema, duodenitis, ileitis
10	5				6 hr.	42 (acid)	7.0	Edema, slight gastritis fundus, severe enteritis (acidity 12/43)
Fed; no infusion; no burn								
11			6	2.5				Slight duodenitis
12			6	3.3				None
Fed; no infusion; burn								
13			2	0.5	4 hr.	2.5	0.6	None
14					5 min.	15-20		None

15					4 hr.	15	4.0	None
16					4 hr.	20	5.0	Stomach contracted and edematous
Fed; infusion; no burn								
17	6		7	0				Stomach mucosa very dry, anterior and posterior walls sticking together
Fed; infusion; burn								
18	7				5¾ hr.	215 (acid)	37.4	Duodenal mucosa edematous and hemorrhagic; pancreas normal (acidity 97/106)
19	5				5¼ hr.	108 (acid)	20.6	Slight duodenitis (acidity 54/91)
20	6				5½ hr.	108 (acid)	19.6	Edema of gastric mucosa (acidity 36/50)
21	6				7 hr.	145 (acid)	20.7	Slight gastritis and duodenitis (acidity 15/29)
22	4				7½ hr.	175	23.3	Food in stomach; edema of gastric mucosa; severe duodenitis and ileitis
Starved; infusion; drugs; burn (except Experiment 23, no burn)								
23*	4†	Histamine	6	14.0				None
24*	4†	Histamine			6 hr.	120	20.0	Gastritis, ulcers, edema
25	4‡	Histamine	2	35.0	4 hr.	24	6.0	Gastritis and edema
26	3	0.5 mg. pilocarpine nitrate intravenously every hour	3½	2.3	6 min. 7 min. 27 min. 45 min. 95 min.	28 2 10 10 30	280.0 17.0 22.0 13.3 19.0	
27	3	As above	3½	2.2	1 min. 30 min.	25 30	(1500) 60.0	
28	4	As above	2	3.5	45 min.	17	23.0	
29	6	0.5 mg. pilocarpine nitrate intravenously every half hour			2 hr.	25	12.5	Gastritis and edema

*Litter mates, same breed, sex, weight.

†5 mg. %.

‡8 mg. % histamine HCl in saline (0.9%)-glucose (5%) solution. Anesthesia with nembutal, except with ether in experiment 6.

TABLE II

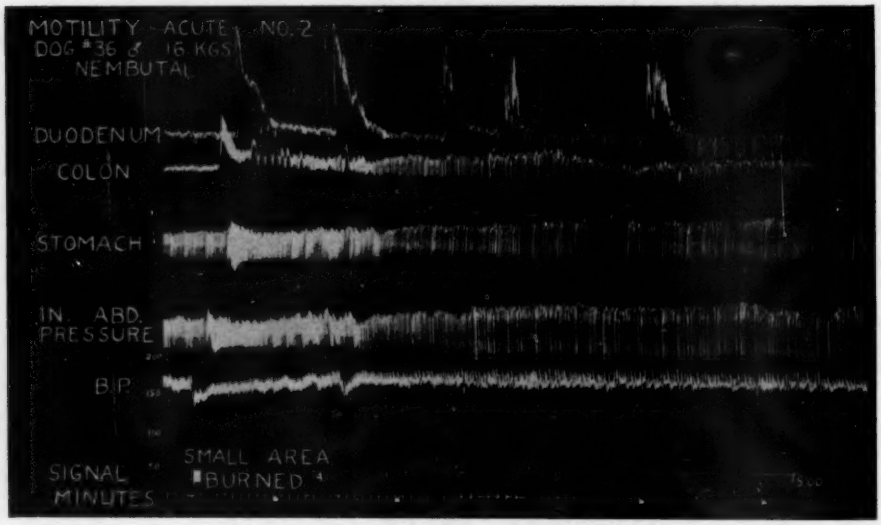
SUMMARY OF GASTRIC SECRETIONS FOLLOWING BURNS

TOTAL NO. OF EXPERIMENTS	PROCEDURE	AVERAGE SECRETION PER HOUR C.C.	NO. OF EXPERIMENTS WITH FREE ACID
10	*No burns,* all experiments*	3.0	0
3	No infusion	2.1	0
7	Infusion	3.4	0
4	*Burns,* fed or starved, no infusion†	3.3	0
7	Starved, infusion	17.4	3 out of 7
5	Fed, infusion‡	24.1	4 out of 5

*Except histamine Experiments (No. 23-25).
†Except Experiments 2 (dog sick) and 14 (died 5 minutes after burn).
‡Except histamine and pilocarpine experiments (No. 23-29).

to 29) similar results were obtained, except in Experiment 25 in which secretion decreased after a burn, although histamine had been given by constant injection.

In the experiments in which pilocarpine was administered (Experiments 26 to 29), surprisingly low volumes of secretion were obtained during the control periods; following burns the volumes rose to a considerable degree, but not acidity.



A.

Figs. 1 *A* and *B.*—Gastrointestinal motility and intra-abdominal pressure following burns. Note increase of intra-abdominal pressure following third burn.

The increase in the rate of volume secretion seemed to be greatest immediately following the burn, sometimes during the first few minutes (see Experiments 4, 26, and 27).

The amount of secretion seemed to be related to the appearance of free acid so far as the presence of free acid accompanied the larger volumes of secretion, but the reverse was not always true. Food in the

stomach may abolish free acidity (Experiment 22). In Experiment 5 only 33 c.c. of an alkaline fluid was discharged from the cannula in the pylorus, but when the stomach was opened it was found to contain 233

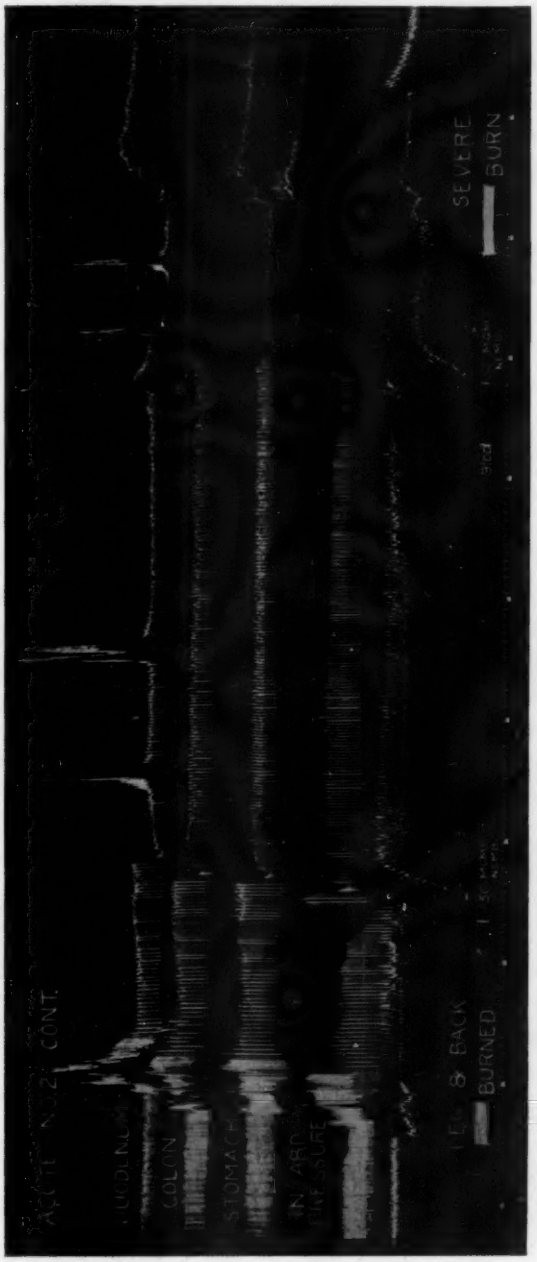


Fig. 1B.

c.c. of secretion with 74 and 85 degrees of free and total acidity. In this dog the presence may be assumed, of a spasm of the musculus sphincter antri, which separated the antrum and the body of the stomach. This assumption is supported by our observations on the

motility of the stomach after burns and by the findings in a case of a burned child. The dog in the above-mentioned Experiment 5 had a prepyloric ulcer and a marked degree of gastritis.

B. Motility.—

In the experiments reported above a great increase in the rate and depth of respiration and a strong contraction of the abdominal wall were noted to follow a burn in animals in a deep state of anesthesia, with absence of the corneal reflex. In the following experiments respiration, intra-abdominal pressure, and gastrointestinal motility were investigated following burns.

In 2 experiments motility of duodenum, colon, and stomach was recorded, together with intra-abdominal pressure and blood pressure. In Experiment 1 a notable increase in intra-abdominal pressure and respiration followed the burn, with little effect on gastrointestinal motility per se, except that produced by intra-abdominal pressure and respiration. The blood pressure in this dog fell very little. In the second experiment (Fig. 1) considerable duodenal motility with strong and prolonged contractions followed the first and second burns. Following a third more severe burn of the legs and the lower part of the back a marked increase in intra-abdominal pressure and an increase in colonic motility were noted. As will be shown below, gastric motility following a burn is strongest in the pyloric antrum, and a stomach balloon will indicate little of this activity.

In order further to analyze gastric motility following burns, 13 experiments were performed, using various procedures. In 2 experiments the abdomen was kept open and the stomach exposed to direct observation. The viscera were kept moist throughout the experiments. In 3 experiments the chest was opened, the phrenic nerves cut, and artificial respiration was administered. In most experiments a balloon was introduced into the pyloric antrum through the pylorus, and in some experiments another balloon was inserted into the body of the stomach through the esophagus. In a number of animals the vagi were cut in the neck and the splanchnic nerves above the diaphragm. A number of animals received 1 to 4 mg. of atropine sulfate intravenously before or following a burn. Blood pressure and respiration or intra-abdominal pressure were recorded. Hemoglobin, hematocrit, plasma CO_2, plasma proteins, and circulating time were determined in most of the experiments.

Fig. 2 demonstrates a typical experiment. During a control period of twenty minutes little antrum motility was apparent. Following the first burn, antrum motility and tone were greatly augmented. Section of both vagi did not abolish antrum motility, but modified it, due apparently to the change in respiration. Following a second burn, an even greater degree of gastric motility occurred; section of the vagi seemed to enhance the motor effects of burns on the pyloric antrum.

The intravenous injection of 2 mg. of atropine sulfate abolished antrum motility completely for about 100 minutes. A slight degree of motility reappeared later, but a third burn failed to evoke the usual motility which was observed in control experiments to follow three or four subsequent burns. Two similar experiments were performed, with identical results.

Section of both vagi and splanchnics did not abolish antrum motility following a burn, and a subsequent burn elicited strong increase in antrum tone and motility.

In 4 experiments simultaneous balloon records from the pyloric antrum and from the body of the stomach were obtained. Motility of the corpus of the stomach was apparent following burns, but it was of lesser degree than that of the antrum. Both were abolished by intravenous injection of 2 to 4 mg. of atropine sulfate, and subsequent burns failed to elicit them.

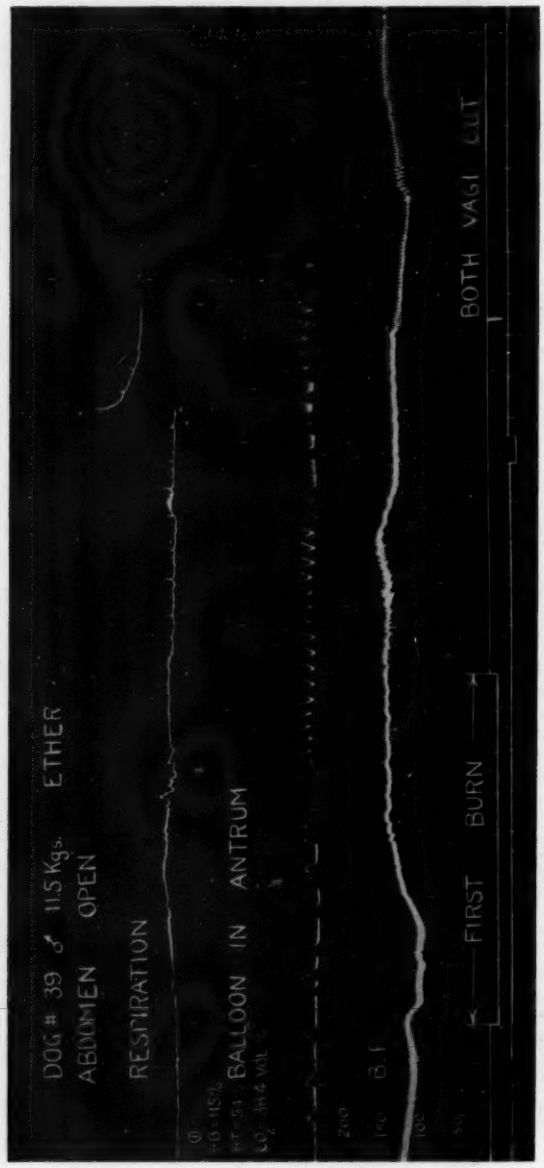
The duration of gastric motility following a burn varied between twenty minutes and two hours. Antrum motility persisted for longer periods of time than motility of the corpus of the stomach.

The experiments in which the stomach had been exposed for observation amplified the above experiences. In one such experiment no gastric motility was seen during a period of twenty-five minutes before the burn. Immediately after the start of the burning, the antrum began to show contractions, followed shortly by the corpus. The entire stomach contracted tonically to about one-half its size. The contractions of the antrum began at the height of the incisura angularis and were regular and forceful, with a rate of one or two per minute, giving the impression of pulsations. The waves of contraction stopped at the pylorus and none were observed to pass into the duodenum. The duodenum contracted tonically. Section of the vagi did not affect gastric motility, but injection of 2 mg. of atropine sulfate abolished motility and relaxed the stomach completely within five minutes. Another burn, applied twenty minutes later, did not evoke gastric motility or increase in tone.

In another similar experiment the first burn produced strong motility of antrum and stomach. A second burn, following section of the vagi, was followed by such forceful antrum motility that the distal part of the antrum was forced over the pyloric canal, giving the impression of an intussusception. Two milligrams of atropine intravenously abolished tone and contractions for ninety-four minutes, after which a third burn caused small increase of tone and shallow ripples of motility mainly of the antrum. Following the first burn, the gall bladder contracted to about one-half its size, but the duodenum did not change.

The effects of atropine were uniform in all 7 experiments in which it was injected. Motility and tone of the stomach, following one or more burns, were either abolished or depressed to shallow ripples.

Intra-abdominal pressure, which was increased in every burn experiment, was not responsible for the gastric motility observed, as proved by experiments with chest opened, phrenics cut, and artificial respiration, and by direct observation. The increased intra-abdominal pressure was due to tonic contraction of the abdominal wall and of the chest, as observed directly and as shown on graphic records.



A.

Figs. 2 *A*, *B*, and *C*.—Respiration and motility of the pyloric antrum following burn. Blood pressure was well maintained throughout experiment. Note appearance of antral motility following first burn. Section of vagi did not abolish motility of first or second burn. Atropine abolished motility of second and third burn completely.

PATHOLOGIC FINDINGS

After burns, a considerable degree of edema of the mucosa and of gastritis and duodenitis was found in a number of animals with small erosions of the gastric and duodenal mucosa in a few animals, and a

prepyloric ulcer in one dog. Histologically this last was a typical peptic ulcer, extending to the muscularis propria.* The duodenitis was present also in animals in which the pylorus had been ligated, so that no gastric juice could have entered the duodenum. The edema of the mucosa of the stomach was particularly striking in those animals which had received intravenous infusion of saline-glucose solution. No macroscopic changes were found in the adrenals.

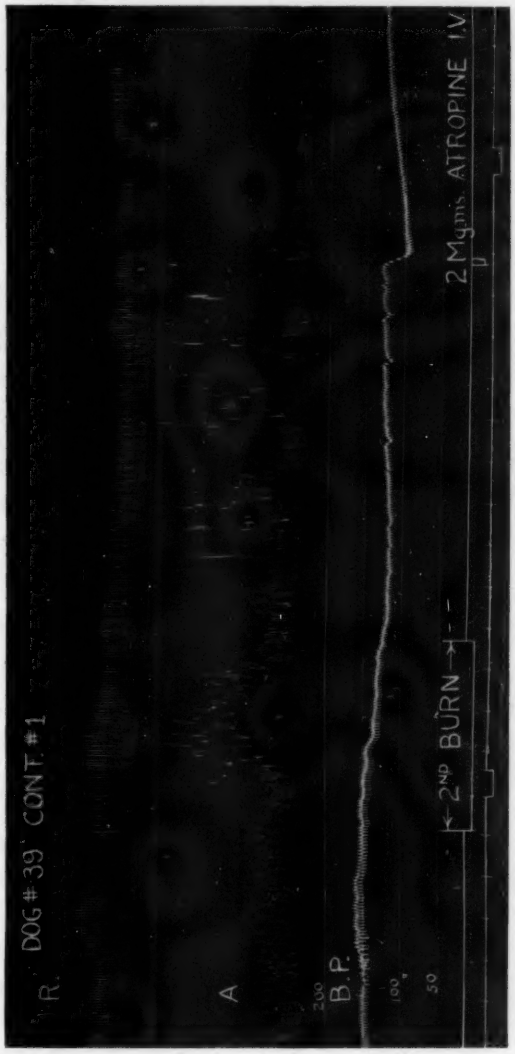


Fig. 2B.

CHEMICAL FINDINGS

No relationship was found between the degree of acidosis and hemoconcentration and the secretory or motor responses following burns. Most animals had blood pressures of 100 and above for the greater part of the experiment, and in nearly all of them the burns did not affect

*We are indebted to Dr. Max Appel from the Department of Pathology for advice.

blood pressure greatly; in a number of dogs blood pressure rose after a burn. Urinary secretion, collected from a ureter or from the bladder in several experiments, showed a decrease of about 50 per cent, as hemoconcentration and acidosis developed. The detailed results of our studies on blood chemistry following shock from burns will appear in another paper by us.

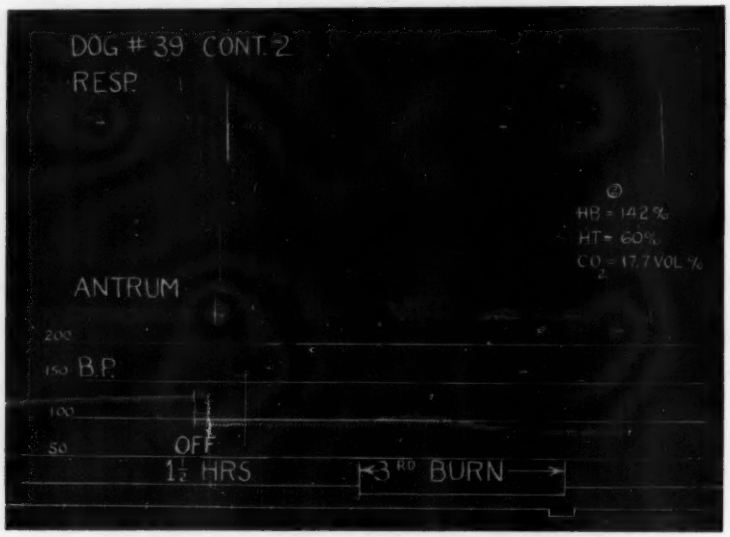


Fig. 2C.

DISCUSSION

Following burns the volume of gastric secretion was found to be increased considerably in those experiments in which a constant intravenous infusion of saline-glucose solution was given. In the experiments without intravenous infusion no appreciable increase in volume of gastric juice was found after a burn. Feeding ten hours before the experiment seemed to result in a larger volume of secretion and a higher incidence of free acidity following a burn than resulted after starving the animal for thirty hours before the experiment. These findings may have a bearing on conditions in the human patient suffering from burns because, except during the early morning hours, the human being is in the absorptive phase of digestion, and because the human patient with burns usually receives large amounts of fluid by mouth or by clysis.

Concerning the increased volumes of secretion following burns observed in our experiments, we have to consider that the forceful contractions of the stomach may squeeze fluid out of the glandular ducts and pockets of the organ. It is hard to believe, however, that this alone can be responsible for such large volumes and continued secretion as followed the burn in a number of experiments.

Evidence is accumulating that histamine or a related compound is liberated in the skin of human beings, dogs, and other animals under the

influence of thermal trauma.[12, 13, 20] It may be that under conditions not known as yet, the absorption of this substance may vary,[21] or that deeper burns may destroy it. The rectal temperature of the dogs was not changed materially following burns. In most animals the legs and thighs were burned, in some the lower part of the back, and in one a superficial burn of the skin of the body was added. We do not believe that the intensity and duration of the burns were sufficient to raise intra-abdominal temperature and thus affect secretions.[1] A raised intra-abdominal temperature would tend to increase biliary secretion in anesthetized dogs.[14]

The increase in gastric motility following a burn cannot be attributed to histamine or like substances for the following reasons: Histamine has little or no effect on gastric motility and the response of the stomach to histamine is not abolished by relatively small doses of atropine. The prompt depressing effect of atropine on gastric motility in our burn experiments points to the presence of compounds of the nature of acetylcholine. These may be liberated by burns, or, more probably, the acetylcholine-splitting esterase may be inhibited following a burn. Acetylcholine injected either continuously or in repeated doses is able to elicit gastric secretion as well as motility,[15, 16, 22] and it is possible that both gastric secretion and motility may be largely stimulated by that one compound. The simultaneous decrease in stimulated salivary (except in one experiment) and pancreatic secretions and the increase in gastric secretion following burns cannot be explained at the present time. We are aware of other observations on shock or diminished blood volume which describe decreased blood flow through the submaxillary gland,[17] vasoconstriction of abdominal organs, varying degrees of capillary resistance in different organs,[18] and varying blood flow through different organs or parts of the body.[19] These observations are not necessarily opposed to our findings, since in our experiments a state of activity of the stomach was evident, and because biogenic compounds can act selectively on different organs. Further studies on this problem are in progress.

Our observations on decreased salivary, biliary, and pancreatic secretions following burns and observations of a considerable increase of gastric secretion and motility together with increased intra-abdominal pressure throw some light on the pathogenesis of Curling's ulcer. Although this type of ulcer becomes clinically apparent much later after the burn, it can be assumed that the local acute pathology begins to develop much earlier.

SUMMARY

The effects of burns on gastrointestinal secretion and motility were studied in anesthetized dogs. Salivary, biliary, and pancreatic secretions were diminished, with the exception of one experiment in

which a considerable increase in salivary secretion was observed. Gastric secretion and acidity increased in a number of experiments following a burn. In one of these animals a prepyloric ulcer was found. Increased volume of gastric secretion seemed to depend on infusions, and increased acidity seemed to be related to infusions and previous feeding of the animals.

A considerable increase in intra-abdominal pressure and of gastric motility was observed following burns; the latter was particularly strong in the pyloric antrum and began immediately after starting of the burn. Section of the splanchnic nerves and of the vagi, or of both, did not diminish or abolish gastric motility following burns. Section of the vagi seemed to enhance the gastric motor response to a burn. The intravenous injection of atropine sulfate abolished the motility of the stomach following a burn. The relation of the above findings to Curling's ulcer are discussed.

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A NERVOUS FACTOR IN THE ETIOLOGY OF SHOCK IN BURNS

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A NUMBER of investigations have been carried out to study the significance of afferent nerve impulses in the etiology of traumatic shock. Crile[1] early pointed out the importance of a nervous factor in shock. O'Shaughnessy and Slome[2] presented convincing evidence that afferent nerve impulses from a traumatized limb play an important role in the production of shock. Lorber, Kabat, and Welte[3] confirmed the observation that shock occurs following trauma to an extremity disconnected from the body except for the main nerve trunks. Freedman and Kabat[4] showed that despite limited fluid loss, trauma results in shock, and further, that the fall in blood pressure can be prevented by preliminary transection of the lumbar spinal cord. In human abdominal surgery, Volpitto, Woodbury, and Hamilton[5] found evidence in arterial pulse curves for a neurogenic type of shock.

While evidence has been accumulating concerning the importance of the nervous factor in traumatic shock, no analysis of the nervous influence in burn shock has been made. Thus, Wilson,[6] in a recent review (1941), states: "Whether noxious nerve impulses from the injured area play any part in initiating or perpetuating secondary shock of burns is unknown." The purpose of the present investigation is to study the significance of a nervous factor in shock following burns.

METHODS

Observations were made on 83 adult cats of both sexes, anesthetized with pentobarbital sodium administered intraperitoneally in doses of 35 mg. per kilogram. Additional barbiturate was given at intervals to maintain such a level of anesthesia that the cat was relaxed, the corneal reflex absent, but the lid closure reflex in response to touching the skin in the neighborhood of the inner canthus remained active. The anesthesia was maintained as long as the animal survived.

In one series of experiments, blood pressure was recorded from a cannula in the carotid artery by means of a mercury manometer, 5 per cent sodium citrate being used as the anticoagulant. The artery was occluded by means of a clamp except when a blood pressure reading

*Aided by a grant from the Committee on Scientific Research of the American Medical Association.

Received for publication, Dec. 18, 1941.

was taken two to three times per hour. In these experiments, the trachea was cannulated. In another series of experiments, no surgery was performed on the neck.

The burn, confined to the skin of one hindlimb, was produced by means of a Bunsen flame. In some experiments, the leg was burned for ten minutes, in other experiments for fifteen minutes.

The saphenous vein of the normal hindlimb was exposed and all blood samples were drawn from this vein by needle puncture. For hemoglobin determinations, 20 c.mm. of blood was drawn into a pipette, diluted with 8 c.c. of 0.1 N hydrochloric acid and the hemoglobin concentration read in a colorimeter. For determination of specific gravity of the blood, 0.0001 c.c. of heparin (Connaught, 1,000 units per c.c.) was placed in the bottom of a small test tube and evaporated to dryness by slight warming. This delayed clotting and facilitated the determination of specific gravity. Fifty cubic millimeters of venous blood was mixed with the dry heparin and specific gravity measured by means of the falling-drop apparatus,[7] two determinations being made on each sample of blood.

In approximately one-half of the animals, afferent impulses from the burned limb were prevented from reaching the brain by preliminary transection of the spinal cord, performed without aseptic precautions, usually thirty minutes before burning. In some animals, the spinal cord was cut at the first lumbar segment, in others at the eleventh thoracic segment. It is recognized that such cord transection has effects other than simple limb denervation, but it is believed that the latter is the most important consequence.

At the termination of the experiment, either following death or sacrifice of the animal, the thoracic and abdominal organs were examined grossly. The hind quarters were carefully separated in the midline and weighed, the difference in limb weights being taken as a measure of the local loss of fluid in the area of the burn.

RESULTS

I. *Blood Pressure.*—The average initial arterial pressure in 14 control cats was 120 mm. Hg. Within several minutes of initiation of thermal trauma, blood pressure had risen abruptly 40 mm. Hg (Fig. 1). During and immediately following the burn the heart rate tended to slow considerably, the pulse pressure increased, and the blood pressure tended to show sharp variations from minute to minute. Several minutes after the burn, the heart rate became rapid and regular and remained so throughout the experiment. The increased blood pressure was maintained for many hours, declining gradually to reach the original level at ten hours.

The average initial blood pressure in 14 spinal cats was 91 mm. Hg. During the period of the burn, in contrast to the experiments on normal cats, the arterial pressure fell sharply, an average of more than

30 mm. Hg as shown in Fig. 1. During and immediately following thermal trauma, the heart became irregular, and slowed in every case, the average heart rate noted at the termination of the burn being 91 beats per minute (54 to 128). Within five to ten minutes after cessation of thermal trauma, the heart became and remained rapid and regular. The blood pressure rose gradually to the initial level in one and one-half hours and did not fall much below this level during the period of observation.

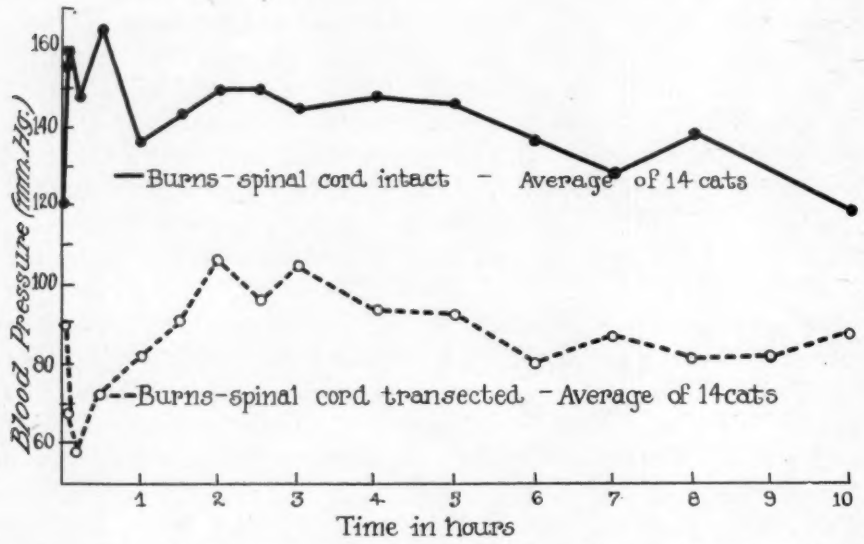

Fig. 1.—Changes in arterial pressure resulting from burns in control and spinal cats. All points are average values.

II. *Hemoglobin.*—In 24 control cats, the initial hemoglobin was 9.69 Gm. per 100 c.c. of blood. Hemoglobin increased sharply as a result of the burn; at thirty minutes the blood had concentrated 34.5 per cent (Fig. 2). After this initial hemoconcentration, hemoglobin continued to rise slowly, reaching a maximal increase of 44 per cent at eight hours. Hemoglobin determinations in 5 cats at twenty-six hours after the burn showed a fall of 25 per cent below the peak value.

The initial hemoglobin averaged 9.96 Gm. per 100 c.c. of blood in 25 spinal cats. Hemoglobin increased much less rapidly as a result of burns in spinal animals (Fig. 2). At thirty minutes, hemoconcentration reached a value of only 14.5 per cent and then increased gradually to reach a maximum of 32 per cent at seven hours. Hemoconcentration in 5 cats twenty-three hours after thermal trauma was 4.1 per cent below the peak value.

No marked change in hemoglobin during the same period was noted in spinal animals which were not subjected to thermal trauma (Fig. 2). At thirty hours, in these experiments, the average hemoconcentration was 9 per cent.

III. *Specific Gravity of Blood.*—The average initial specific gravity of whole venous blood in 24 cats measured by the falling-drop technique, using the heparin method described above, was 1.0471.

The sharp initial rise in specific gravity following thermal trauma in control cats and the slight further increase with time are shown in Fig. 3. The specific gravity of the blood increased an average of 0.0106 within twenty minutes after the burn and attained a maximal increase of 0.0127 at three hours. After a longer interval, the specific gravity tended to decrease considerably, falling at twenty-five hours to an average of 0.0066 below the peak value in several experiments.

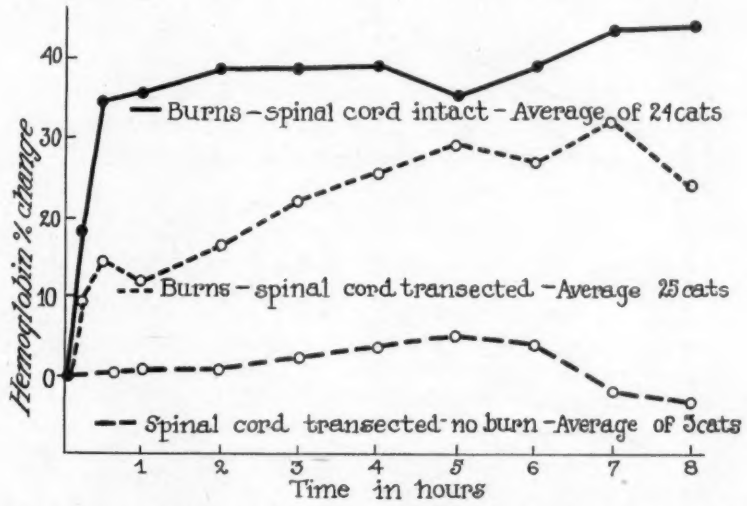

Fig. 2.—Percentage increase in concentration of the blood resulting from burns as demonstrated by hemoglobin determinations in control and spinal cats. All points are average values.

The blood concentrated more slowly and to a lesser extent following burns in 13 spinal cats (Fig. 3). Specific gravity increased only 0.0027 at twenty minutes and attained a maximal rise of 0.0066 at four hours. At twenty-four hours, the specific gravity was found to be 0.0003 below the maximum.

IV. *Respiration.*—The changes in respiratory rate resulting from burns in 14 control cats are shown in Fig. 4. The rate of respiration rose sharply during burning, and continued to rise for some time afterward, reaching a maximum of 36 per minute at two hours. Even at six hours, however, the respiratory rate averaged 29.5 per minute, considerably above the initial value.

In 12 experiments on spinal animals, the respiratory rate showed a greater rise following burns than in cats with the spinal cord intact (Fig. 4). Respiratory rate rose within fifteen minutes after initiation of thermal trauma to 42 per minute. The maximal respiratory rate of 47 per minute was noted at two hours, following which the rate of respiration declined.

V. *Temperature.*—The rectal temperature before the burn averaged 98° F. in 29 control cats. The average increase in body temperature recorded immediately after the burn was 4.2° F. The temperature began to fall soon after thermal trauma was terminated and continued to fall progressively.

In 30 spinal cats, body temperature averaged 97° F. before the burn with a range from 92 to 100° F. Immediately after thermal trauma, the rectal temperature increased an average of 4.2° F. to 101.2° F. (92.6 to 110° F.).

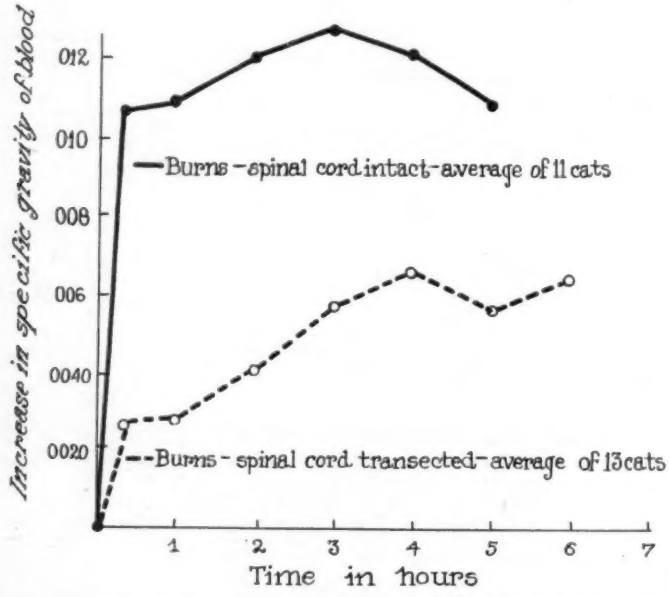

Fig. 3.—Hemoconcentration following burns as demonstrated by measurements of the specific gravity of the blood by the falling drop technique in control and spinal cats. All points are average values.

VI. *Survival.*—The extreme variability of survival time after burning has made a quantitative study of the effect of spinal transection difficult. Survival was studied in selected cats in which blood pressure was not recorded and no surgery was performed on the neck. Also, cats which died acutely within one hour of burning were not considered in the analysis of survival. In all of these experiments, one hindlimb was burned for fifteen minutes. In 24 normal cats, survival ranged from one and one-half to eighty hours. The average survival in this series was thirty-two and one-half hours and the median survival thirty-four hours. In 19 cats with the spinal cord transected at the eleventh thoracic segment, the average survival following the burn was forty hours, the median forty-one hours, and the range was ten to seventy-five hours. The apparent increased survival following burns in the spinal cats was 23.1 per cent if one considers the average values

and 20.6 per cent if one considers the median values. There is thus a possible small increase in survival after cord transection.

Of special interest is the fact that a number of animals died during or immediately after burning: 9.3 per cent of all control cats and 6.9 per cent of the spinal cats. In all of these cases the respiration stopped suddenly during the burn, the heart was slow and irregular, and artificial respiration did not result in recovery, although the heart continued to beat for some time. The blood pressure was very low at the time respiration stopped in spinal animals. The local fluid loss in the burned limb averaged 1.15 per cent of the body weight, and hemoglobin was only 5 per cent above the initial level at the time of death. In one instance, respiration stopped during thermal trauma and after removal of the flame for one minute, spontaneous respiration was resumed; continuation of the burn for a total of fifteen minutes did not cause a further crisis and the animal survived for ten hours.

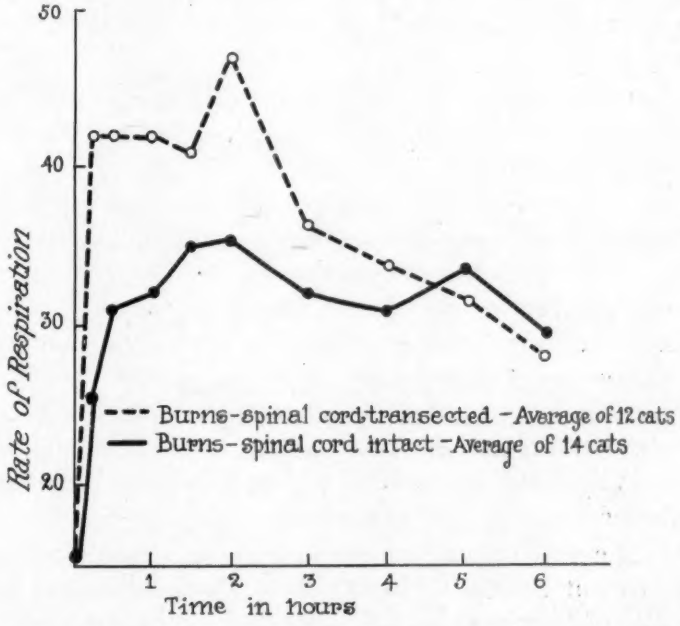

Fig. 4.—Changes in respiratory rates following burns in control and spinal cats. All points are average values.

VII. *Local Fluid Loss.*—The average local fluid loss in the burned limb in 14 control cats was 2.5 per cent of the body weight. The average maximal hemoglobin increase was 45 per cent. The local fluid loss did not correlate very closely with survival time or hemoglobin concentration. In 10 cats sacrificed at an average time of fourteen and one-tenth hours following the burn (six and one-half to thirty-four hours), the local fluid loss was 2.9 per cent of the body weight and the average maximal hemoglobin increase was 42.4 per cent. On the other

hand, in 4 cats which died from the burn in an average of ten and two-tenths hours (one to twenty-one hours), local fluid loss was 1.6 per cent of the body weight and the maximal hemoglobin increase was 55 per cent.

Local fluid loss in the burned limb was 1.5 per cent of the body weight in 14 spinal cats and the maximal hemoglobin increase 25 per cent. Seven of these cats, which were sacrificed in an average of nineteen hours (eleven to thirty hours) had a local fluid loss of 2.2 per cent, and a maximal hemoglobin increase of 24 per cent. In 7 other cats which died from the burn in an average of ten and six-tenths hours (ten minutes to sixteen hours), the local fluid loss was only 0.96 per cent, while the maximal hemoglobin increase was 26 per cent.

VIII. *Pathology.*—Observations on gross pathology were made after burns on 38 control cats and 35 spinal cats. In the burned hindlimb, the skin was contracted, dry and leathery, and split in one or more places. The subcutaneous tissue was markedly edematous. The superficial veins were all thrombosed and contained a dark brown, semisolid coagulum.

The data on pathology of the internal organs are summarized in Table I. It is noteworthy that a greater percentage of the spinal cats showed pathologic changes in the lungs, kidneys, urinary bladder, heart, stomach and duodenum, and liver. The lesions were, however, no more severe in the spinal animals. As will be evident from the table, most of the cats showed pulmonary and renal congestion and dark, bloody bladder urine. Other frequent lesions were subendocardial hemorrhages in the left ventricle, clots in the right ventricle, and acute hemorrhage or ulceration in the pylorus or duodenum. The liver was not infrequently discolored, soft and friable; the spleen large, dark purple, and congested. In a number of cases, the myocardium had a violet tinge and appeared to be degenerating. In several cats, the anterior mediastinum was hemorrhagic.

Emphasis should be placed on the fact that pericardial effusion was a very infrequent finding. Pleural effusion or ascites was never observed in any of the animals. The intestines were not edematous, congested, or distended with fluid and in most instances appeared quite normal. The low incidence of adrenal pathology is also worthy of mention.

In 5 cats which died acutely during or immediately following thermal trauma, the pathology is listed in Table I. All showed pulmonary congestion; 2 moderate and 1 marked congestion. The urine was normal, the kidneys little affected. The spleen was large, dark, and congested. There was a good deal of cardiac pathology. In 2 instances, the brain was carefully examined but there was no pathology to account for the sudden arrest of respiration.

TABLE I

GROSS PATHOLOGY OF EXPERIMENTAL BURNS

		SPINAL CORD INTACT (38 CATS)	SPINAL CORD TRANSECTED (35 CATS)	ACUTE DEATHS (5 CATS)
Lungs	Slight congestion	31%	63%	40%
	Moderate congestion	13%	11%	40%
	Marked congestion	16%	11%	20%
	Total congestion	60%	85%	100%
Kidneys	Slight congestion	16%	20%	20%
	Moderate congestion	10%	37%	
	Marked congestion	34%	20%	
	Total congestion	60%	77%	
Urinary bladder	Urine			
	Normal	21%	22%	100%
	Bloody	79%	78%	
	Submucous hemorrhage in bladder	10%	30%	
Heart	Subendocardial hemorrhage left ventricle			
	Slight	16.0%	28%	20%
	Moderate	2.6%	14%	
	Marked	16.0%	11%	20%
	Total	34.6%	53%	40%
	Clot in right ventricle	30.0%	31%	40%
	Clot in left ventricle	8.0%	11%	20%
	Bloody pericardial fluid	2.6%	2.8%	
	Clear pericardial fluid		2.8%	10%
Stomach and duodenum	Submucous hemorrhage, pylorus	8.0%	2.8%	
	Hemorrhage and ulcer, pylorus	2.6%	5.6%	
	Ulcer, pylorus		11.0%	
	Submucous hemorrhage, duodenum	10.0%	5.6%	20%
	Ulcer, duodenum	2.6%	2.8%	
	Total	23.2%	27.8%	
Adrenals	Hemorrhage	16.0%	8.6%	
	Congestion	2.6%	8.6%	
Liver	Punctate hemorrhages	0	14%	20%

DISCUSSION

Despite the fact that one of the established procedures in the therapy of clinical burns is the administration of morphine for the relief of pain, very little attention has been paid to the role of a nervous factor in shock following thermal trauma. In his review on burns, Harkins[8] declared: "A purely nervous theory of causation of shock and death in burns is not generally held. This is quite contrary to the case with traumatic shock in general where many workers support a purely nervous theory." Wilson[6] noted that nothing is known about the influence of noxious nerve impulses in burn shock. However, the general clinical impression has been that relief of pain in burns is of value in combating shock.[9]

The only previous experimental study of a nervous factor in burns was reported in 1858 by Brown-Sequard.[10] He stated in a lecture in England: "In two cases, on animals in which the trunks of the sciatic

and crural nerves in one limb had been divided as high as possible, I have not found a state of marked congestion in any viscus, three days after I had carbonized this limb from the toes to the middle of the thigh." He also found an absence of visceral pathology following burns of one leg in animals in which the spinal cord had been divided at the third or fourth lumbar segment. On the other hand, visceral congestion was observed following burns in animals with the spinal cord transected at the third thoracic segment. "From these experiments and the preceding, it results that it is, in a great measure, by a reflex action of the spinal cord, that burns produce their deadly influence on the viscera." Brown-Sequard also recognized the importance of other factors: "Of course, it is not by reflex action only that some of the phenomena mentioned in this lecture are produced. . . . . In a case of extensive burns, for instance, there are several circumstances which contribute to the production of the visceral alterations. . . . ."

In the present study, it has been possible to demonstrate a nervous factor in burn shock even under surgical barbiturate anesthesia. The type of experimental procedure employed necessitated the use of surgical anesthesia in this investigation. While it is difficult to predict the exact significance of the nervous factor in the unanesthetized animal, it is probable that afferent nerve impulses exert a more potent influence under those conditions. While the nervous factor may not be the major factor in determining a lethal outcome, it nevertheless plays a significant contributory role in the shock which follows thermal trauma.

Transection of the spinal cord at the first lumbar segment effectively prevents the initial and to some extent the sustained rise in blood pressure which results from thermal trauma. Since practically the entire sympathetic vasomotor pathway remains intact when the spinal cord is divided at this level, spinal transection must eliminate the rise in arterial pressure by cutting off afferent nerve impulses from the burned area presumably activating the sympatheticoadrenal system. It is noteworthy that stimulation of superficial nerve endings in the hindlimb by a burn produces a reflex rise in arterial pressure, while stimulation of the nerve endings in deeper tissues by fracture of the long bones elicits a fall in blood pressure.[3] Since both pressor and depressor fibers run together in the large nerve trunks, one would expect on stimulation of such nerves that the opposing pressor and depressor influences would more or less neutralize one another. These facts may help to explain the failure of many investigators[12] to produce shock by experimental stimulation of nerves.

An initial sharp fall in arterial pressure during and following thermal trauma occurs in spinal animals; this fall is related to toxic and fluid loss factors and is ordinarily masked by the pressor reflex. Since the blood pressure rises slightly above the original level during the period

from two to five hours after the burn in the spinal cat, there must be a nonnervous pressor influence during this period which contributes to the sustained rise in blood pressure in the normal animal. The close correspondence of the general directions of the arterial pressure curves of normal and spinal animals after the first hour following burns is also of interest (Fig. 1).

The most interesting effect of elimination of the nervous factor in burns is the marked decrease in hemoconcentration demonstrable by both hemoglobin and blood specific gravity measurements. Hemoconcentration is considerably less and also increases more slowly in burned spinal cats (Figs. 2 and 3). Local fluid loss in the burned area is also less in spinal animals. The increased hemoconcentration resulting from the nervous factor may perhaps be accounted for by the higher arterial pressure, reflex contraction of the spleen, vasoconstriction, and adrenalin secretion. The influence of a reflex rise in arterial pressure on blood volume is negligible in normal animals, as shown by Gregerson,[13] but may be greater in burns due to the capillary injury. A higher filtration pressure would explain the greater local fluid loss in the burned animal with intact spinal cord. Animals with the spinal cord transected at the eleventh thoracic segment and no burns showed a negligible and very gradual hemoconcentration (Fig. 2). Treat[14] has demonstrated that acute transection of the spinal cord at the eighth cervical segment in cats, with a fall in blood pressure of 40 per cent, resulted in an increase of plasma volume of only 5 per cent. Contraction of the spleen is probably also important in exaggerating the hemoconcentration following burns in control animals. Keeley, Gibson, and Pijoan[9] reported increases of circulating erythrocyte volumes of 59.5, 24.6, and 22.3 per cent in normal dogs, and decreases of 27.8, 13.1, and 7.8 per cent in splenectomized dogs, as a result of extensive burns. There was also a smaller rise in hemoglobin in the splenectomized dogs. On the other hand, they reported a greater decrease of plasma volume and of total blood volume in the burned splenectomized animals.

While the survival time following the burn was apparently increased slightly by preliminary spinal transection, one cannot be certain that this is a valid conclusion, considering the extreme variation in the survival data.

CONCLUSIONS

1. (a) In control cats, thermal trauma results in an immediate rise in blood pressure which is sustained for many hours. (b) In spinal animals, there is a temporary fall in blood pressure followed by a lesser rise as a result of the burn.

2. Hemoconcentration following a burn is less in spinal animals.

3. Spinal transection decreases local fluid loss in the area of the burn.

4. The increase in respiratory rate resulting from the burn is greater in spinal animals.

5. There is no significant difference in visceral pathology in control and spinal animals following burns.

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HEMORRHAGIC CYSTS OF THE LUNG: REPORT OF TWO CASES IN WHICH MARSUPIALIZATION WAS DONE

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FONTANUS wrote to Cl. Plempius, in 1638, the first recorded description of a patient who had a presumed congenital cyst of the lung. This appeared in a report (*De Pulmonibus*) by Thomas Bartholinus of three such cases which were published in 1687 in Malpighius' *Opera omnia*. Excerpts from the translation by Oughterson and Taffel are very interesting:

"A new case, and a rare one in mankind, of a boy without the ordinary lung—a case observed by N. Fontanus and favorably commented upon by ourselves—amply confirms the new observation of Malpighius. . . . The four-year-old boy died, brought to his end by marasmus. Out of interest in the matter I dissected the body, observing that the liver was above the ordinary size. It had an abscess near the vena cava, which was covered with pus all around about the humped portion; a spleen of good color, and unaffected; no omentum or at least none was readily visible. And strange to relate, there were no lungs, but in their place was a membranous vesicle filled with air. This vesicle was provided with small veins and arose from the rough artery [trachea] itself; the vesicle seemed to carry the cooling effect to the heart. Fontanus wrote this to Cl. Plempius on December 20, 1638. He in turn, in his answer of December 29, judged the membranous vesicle to have occupied the place of a lung, since it could receive outside air for cooling the heart by virtue of the fact that it started from the rough artery. But because it did not furnish enough air to the heart, and because the heart could not easily enough be cleansed of its soot, the learned Plempius suspects that therefore the youth fell into this marasmus, the heat of the heart being too intense and almost burning up the body."

Koontz in 1925 called the attention of American physicians to the disease in question by his review of 108 reports of cases collected from the foreign literature, chiefly German. Schenck, in July of 1937, was able to gather a total of 381 reports of cases from the world literature on the subject. Wood[19] in August of the same year reported an additional forty-eight cases in which the patients had been seen at the Mayo Clinic. Since that time numerous isolated reports of cases and groups of cases have appeared in various journals.

ETIOLOGIC ASPECTS

The obscureness of the cause of cystic disease of the lung is indicated by the number of theories evolved to explain its genesis. The scope of

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Received for publication July 23, 1941.

the present paper is too limited to enter into such an inquiry. Suffice it to say that cystic disease of the lung has been attributed to congenital malformations, neoplastic changes, dilatation of the lymphatic vessels, congenital syphilis, congenital bronchiectasis, inflammation within the bronchi during intra-uterine development, bronchopneumonia, and other conditions. It is reasonable to suppose, with Oughterson and Taffel, that pulmonary cysts are similar to cysts of other parenchymatous organs of the body and that, like such cysts, they may be congenital, infectious, mechanical, or neoplastic in origin.

SYMPTOMS

Unfortunately, there are no symptoms which are characteristic of cysts of the lungs. Indeed, a large pulmonary cyst in many cases may be discovered only at post-mortem examination or on the occasion of routine roentgenologic examination of the thorax. However, most authors, such as Taylor, Wood,[18, 19] Schenck, King and Harris and others, have agreed that among children and infants recurrent attacks of dyspnea and cyanosis should make the physician suspect cystic disease of the lungs. Among adult persons the disease usually is manifested because of some complication. If the cyst becomes infected (or if cysts become infected) fever, cough, and expectoration result. Rupture of an air cyst into the pleural space results in formation of the clinical picture of spontaneous pneumothorax. Cysts which have a valvelike mechanism may enlarge sufficiently to produce symptoms arising from compression and distortion of the mediastinal structures. Hemoptysis is a frequent symptom. This symptom, together with the observation of cavitation in the thoracic roentgenogram, has led to the sending of many patients into a sanatorium with the diagnosis of "tuberculosis." Three of Hennell's eight patients gave as their chief symptom recurrent episodes of hemoptysis. Hemoptysis was a prominent symptom in fifty-two of 381 reports of cases collected by Schenck.

DIAGNOSIS

The diagnosis of cystic disease of the lung can be made only after satisfactory roentgenologic study of the thorax has been made. In addition to these, bronchoscopic examination, the injection of radiopaque oil, and performance of diagnostic pneumothorax may be necessary.

Wood[18] emphasized the extreme difficulty of distinguishing fluid-containing cyst from (1) thoracic tumor, (2) pulmonary abscess, (3) empyema, (4) dermoid cyst, and (5) echinococcus cyst. At times the distinction between a fluid-containing cyst and a solid tumor can be made only by exploratory thoracotomy.

TREATMENT

The proper management of patients who have cystic disease of the lung is extremely difficult and various methods have been devised to

meet the different problems that arise in such management. It is generally agreed that those cysts which are accidentally discovered and which are producing no symptoms require no treatment. The crises of dyspnea and cyanosis which occur among young children and infants as a result of large balloon cysts may necessitate repeated aspiration of air from the cyst. Pearson has reported a case in which an 18-month-old child was cured by repeated aspiration. Croswell and King have written of a patient who was benefited by repeated aspiration and, on one occasion, the injection of radiopaque oil into the cyst.

Miller and Lillienthal have inserted one-way "flapper-valve" tubes through the thoracic wall in an effort to prevent the recurrence of increased pressure within the cyst. Bronchoscopic aspiration followed by the injection of iodized oil has been beneficial to a few patients. Wood[18] reported a case in which a patient remained in good health for ten years after thoracotomy and cauterization of the bronchial openings into the cyst. Results of cauterization of the bronchus leading to the cyst through the bronchoscope have been inconstant. Oughterson and Taffel think that this procedure is contraindicated, because it may only partially occlude the bronchus and thus make the condition worse by prevention of the escape of trapped air from the cyst. They recommend introduction of a catheter into the cyst of which the walls have been previously scarified. Negative pressure is then established in the hope of re-expansion of the lung, which will adhere to the thoracic wall. The treatment of choice in cystic disease of the lung would of course be removal of the affected tissue. This may be accomplished by either lobectomy or excision of the cyst. Harrington[5] successfully removed a cystic azygous lobe from the posterior portion of the mediastinum. He also reported[6] on a young married woman, 19 years old, from whom he removed a large intrathoracic cyst which contained clotted blood. She remained well after this procedure. Sauerbruch was able to extirpate the cyst or to perform lobectomy for six patients. One of these died of postoperative shock; the rest were cured. Lee and Harris found reports by Miller, Zdansky, Melchior, Braeuning and Clairmont on patients from whom such cysts were removed in toto with gratifying results.

When patients are encountered from whom removal of the cyst is impossible, marsupialization may result in benefit. Eloesser operated on a male student, 20 years old, who had suffered from what was thought to be chronic empyema for eleven years. At the first operation multiple infected cysts of the left lower lobe of the lung were uncapped and marsupialized. At a second operation a large air-containing and fluid-containing cyst of the upper lobe was drained. The third procedure constituted removal of the sacculated lower lobe. The patient made a good recovery and, except for development of a minute bronchial fistula, seemed well thereafter, although he did not gain weight. The upper cystic cavity remained empty and produced no symptoms.

Neuhof reported a case in which a woman 30 years old was thought to have empyema. At operation a well-defined hemispheric bulge of the right lower lobe was noted. On the assumption that this bulge was caused by an abscess of the lung, this part of the lobe was packed off from the remainder of the pleural cavity and the wound was packed. Pus obtained by aspiration proved to be sterile. At a second operation the lung was entered and a large amount of pus was evacuated from a smooth-walled cyst which communicated with a bronchus. The cyst was lined with ciliated epithelium of bronchogenic character. The postoperative course of the patient was satisfactory and at the time of Neuhof's report the cavity would hold only 10 to 15 c.c. of fluid.

Adams and Swanson recorded a case in which a 45-year-old woman had complained of a productive cough which she said had been present for five years. Roentgenologic study revealed a large fluid-containing and air-containing cyst of the right lung. A two-stage operation similar to the one previously described herein was performed. After drainage of the cyst, the productive cough disappeared. However, if the external opening of the cyst became occluded the patient would again begin to cough. The cavity failed to decrease in size during the period of observation of this patient.

We have two cases of our own, involving cysts of the lung, which we wish to present herein.

REPORT OF CASES

CASE 1.—A man 34 years old registered at the Mayo Clinic on January 30, 1940. He complained chiefly of dyspnea of seven months' duration. In July, 1939, while sitting quietly in a theater, he had experienced sudden severe substernal and epigastric pain associated with intense dyspnea. He had been rushed to a local hospital, where thoracentesis was immediately done. Several hundred cubic centimeters of bloody fluid were removed from the left hemithorax. After removal of this fluid the marked dyspnea subsided, but the patient failed to regain his former respiratory reserve. Further careful study revealed areas in the left part of the thorax which were interpreted as being aneurysmal sacs or neoplasms. In October, 1939, he was able to return to his work in a printing business, but he continued to experience pain in the left costovertebral region and began to cough up clots of old blood. This continued for six weeks. He remained dyspneic and the dyspnea occurred after slight exertion.

A review of this patient's history disclosed nothing of significance in relation to his illness, except for the occurrence of an attack of "pleurisy" when he was 18 years old. This attack had consisted of slight pain in the left portion of the thorax which had inconvenienced him for only a short time.

On examination the patient was found to weigh 138 pounds (62 kg.). His normal weight was 150 pounds (68 kg.). The systolic blood pressure was 150, and the diastolic pressure was 100, expressed in millimeters of mercury. A small adenoma of the thyroid gland was present. Litten's sign was absent on the left and percussion revealed a region of dullness extending from the fourth thoracic vertebra inferiorly on the left side of the thorax. Breath sounds were decreased over this region. Roentgenologic examination demonstrated two large circumscribed shadows involving the greater part of the left side of the thoracic cavity

(Fig. 1*A* and *B*). These were thought to be independent of the large vessels. Bronchoscopic examination revealed some degree of compression of the left lower lobe bronchus, caused apparently by an extrabronchial tumor mass. Tissue removed from this region was inflammatory in nature. Results of repeated examinations of sputum were entirely negative for tuberculosis, and the electrocardiogram disclosed nothing abnormal. The urea measured 14 mg. per 100 c.c. of blood and the sedimentation rate was 21 mm. per hour. Urographically, there was no evidence of polycystic disease of the kidneys. The rest of the routine laboratory examinations, including the flocculation test for syphilis, gave negative results.

A diagnosis of intrathoracic tumor of indeterminate nature was made and surgical exploration was advised.

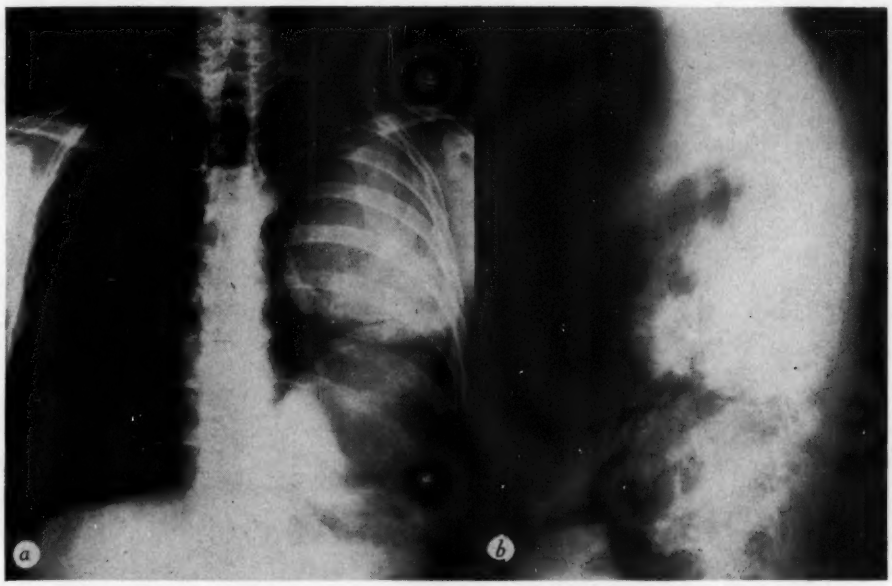

Fig. 1 (Case 1).—Two large circumscribed shadows involving the greater part of the left lung and the left half of the thoracic cavity; *A*, anteroposterior view; *B*, lateral view.

On February 20, 1940, thoracotomy was performed with the patient under the influence of anesthesia produced by cyclopropane administered intratracheally. The incision was made on the left, along the eighth interspace posterolaterally and extending below the angle of the scapula (Fig. 2*A*). The eighth and ninth ribs were cut near their angles and an incision was made between them into the pleural cavity. On opening the pleural space two large globular masses were seen (Fig. 2*B*). These were separated partially from the parietal pleura with some difficulty. The lower tumor seemed definitely cystic and a needle was inserted into it. Thin, brown, bloody material was obtained. The upper mass seemed to be more solid in consistency and the aspiration needle produced thick, brown, chocolate-like material. This mass was then incised and approximately 400 c.c. of the thick, chocolate-like material was evacuated from it. It was found to be a cyst, the lining of which was perfectly smooth. The cyst was roughly round and was approximately 20 cm. in diameter. It did not communicate with the lower cyst; the lower cyst was therefore incised. The lower cyst contained thin, serosanguineous fluid, and was approximately the same size as the superior cyst. It seemed impossible to remove these structures because they evidently arose in the substance of the lung. The lung itself was markedly compressed medially and anteriorly. Performance

of pneumonectomy was considered to be impossible because of the number of dense adhesions existing between the parietal and visceral pleura. It was therefore decided to marsupialize the cystic cavities. They were made to communicate and the edges were brought up to the parietal pleura and attached throughout their circumference with multiple interrupted catgut sutures to the soft tissues of the thoracic wall (Fig. 2*C*). Approximately 8 cm. of the eighth and ninth ribs were

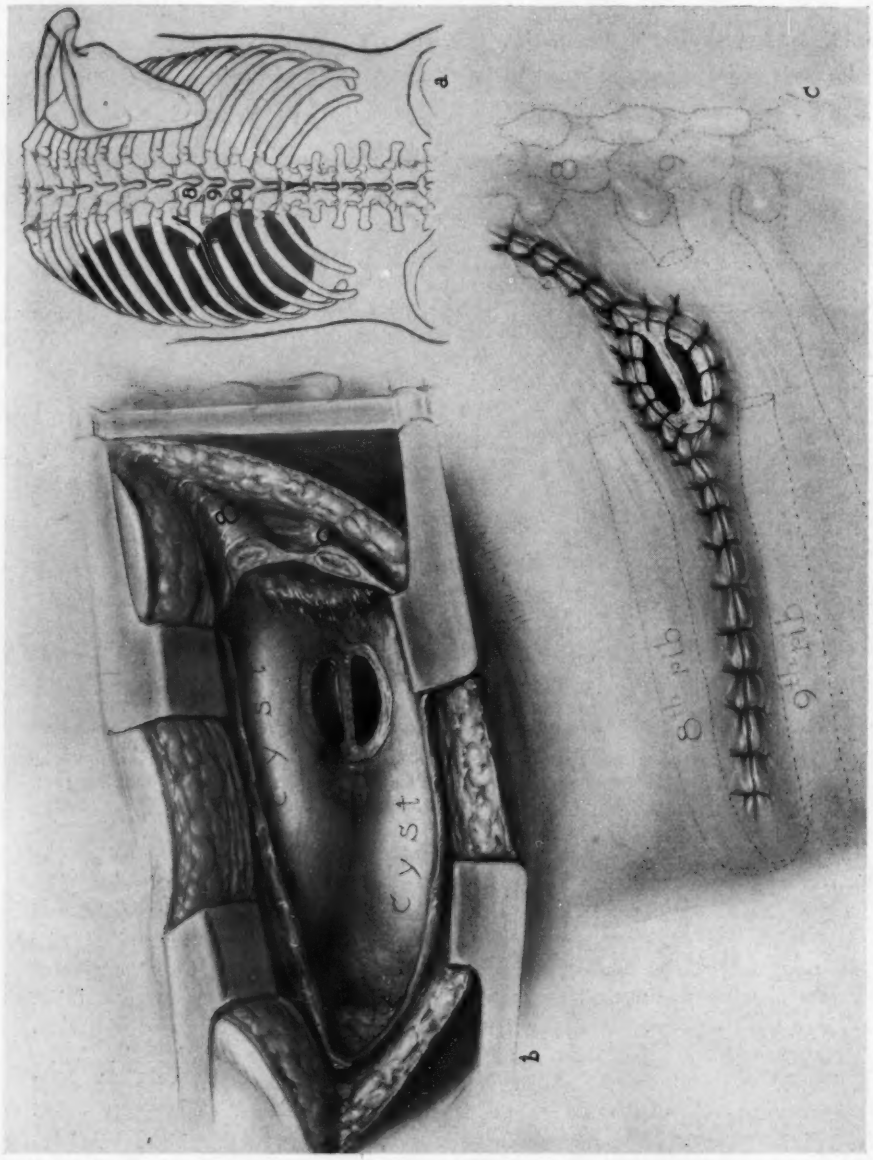

Fig. 2 (Case 2).—Surgical procedure involved in marsupialization of two hemorrhagic cysts of the left lung; *A*, an incision was made along the eighth interspace on the left, posterolaterally; *B*, partial resection of the eighth and ninth ribs near their angles; *C*, two large independent hemorrhagic cysts have been made to communicate and marsupialization of the two cystic cavities has been accomplished.

removed to permit this procedure (Fig. 2*C*). The cystic cavities were then packed with petrolatum gauze. A portion of the cyst wall was removed for microscopic examination and proved to be fibrous hemorrhagic inflammatory tissue with deposition of hemosiderin (Fig. 3).

The patient was returned to his room in excellent condition and was immediately placed in an oxygen tent. His course was not unusual until the fifth postoperative

day, at which time he began to have a septic type of fever. At subsequent thoracentesis a collection of fluid was found anterolaterally on the left. The *Streptococcus haemolyticus* and the *Staphylococcus aureus* were cultured from this fluid. The patient received 2-sulfanilamido-4-methylthiazole (sulfamethylthiazole) with benefit. Examination of the lower cystic cavity on the fourteenth postoperative day revealed a bronchial opening in the depths of the cavity. Since the septic fever continued, it seemed necessary to institute open drainage of the empyema cavity. This was accomplished by removal of a portion of the fifth and sixth ribs, anterolaterally. The patient then began to improve rapidly and he was able to leave the hospital on the thirty-first postoperative day. Three months later his physician at his home reported that the patient was feeling well. The roentgenograms, which the patient's physician was kind enough to send to us, showed considerable clearing of the exudate and diminution of the pleuritis which had been present at the last time a roentgenogram had been made of the patient's thorax at the clinic. The right portion of the diaphragm was elevated by pleuritic adhesions. The cystic cavities were somewhat decreased in size.

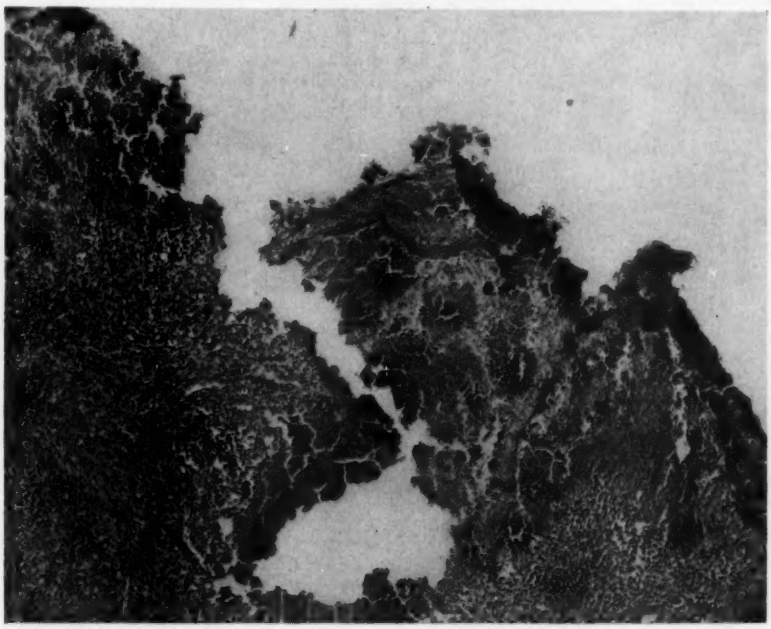

Fig. 3 (Case 1).—Section of the wall of a hemorrhagic cyst of the lung. There was no specific lining to this cyst. The wall was composed of inflammatory fibrous tissue, and the surface was covered with blood (hematoxylin and eosin ×45).

CASE 2.—A man 26 years old registered at the clinic on January 27, 1941. He stated that he had been accepted for military service on December 27, 1940. While he was hunting a week later he was running fast in a high, cold wind and the next day he coughed up blood. He also had some pain in the left shoulder. Since that time he had been coughing up old blood and it had been necessary for him to stay in a local hospital for two weeks. He gave a history of having had pleurisy on the left side five years prior to his registration at the clinic.

On examination he was found to have a blood pressure of 125, systolic, and 80, diastolic, expressed in millimeters of mercury. His temperature was 98.6° F. (37° C.). Examination of his thorax showed the breath sounds to be decreased

in the upper part of the thorax on the left and there was marked dullness over the same area as far down as the third rib. A diagnosis of cyst of the lung had been made previously, elsewhere.

Urinalysis disclosed a specific gravity of 1.010. The reaction was acid. Pyuria of grade 1 (on the basis of 1 to 4) was present. The content of hemoglobin was 12.5 Gm. per 100 c.c.; erythrocytes numbered 4,060,000, and leucocytes 9,000, per cubic millimeter of blood. A differential count gave the following results: lymphocytes 15.5, monocytes 6.0, neutrophils 76.0, eosinophils 2.0, and basophils, 0.5. Anteroposterior and lateral roentgenograms of the thorax, made with a Bucky diaphragm, revealed a large, homogeneously dense tumor mass in the upper, posterior part of the thorax on the left, extending upward from just below the sixth rib to about the second rib (Fig. 4*A* and *B*). There was some erosion of the inferior margin of the fifth rib at the angle. The trachea was slightly displaced to the right. Results of Casoni tests for echinococcosis were negative. Reaction of the complement fixation test for echinococcosis was negative.

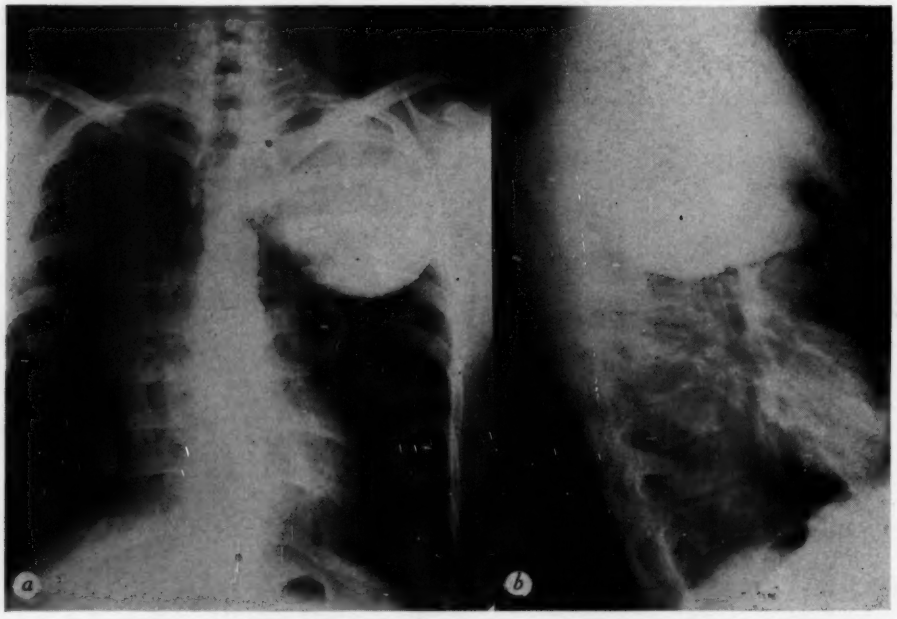

Fig. 4 (Case 2).—A dense tumor mass in the upper, posterior portion of the thorax on the left; *A*, anteroposterior view; *B*, lateral view.

A diagnosis of cyst of the upper lobe of the left lung, with secondary hemorrhage into the cyst, was made. Surgical treatment was advised and the patient underwent operation on January 28, 1941. A curved incision was made along the medial border of the scapula, extending from nearly the upper border of the scapula well laterally. Portions of the fourth and fifth ribs were removed near their angles. An intercostal incision was made in the fourth interspace and a large, rather indurated mass could be seen in the substance of the upper portion of the left lung. The left lung was densely adherent to the parietal pleura and could not be separated except in a very small region; it seemed to be densely attached medially and anteriorly, and it seemed that any attempt to remove it would have imposed more risk than was warranted. The aspirating needle was inserted into the cyst, and dark, bloody material was aspirated. It seemed advisable to drain the cyst, marsupialize the edges and hope that with re-expansion of the lung

the space occupied by the cyst would be obliterated. It was impossible to marsupialize and drain the cyst in the region in which exploration had been carried out, because of the scapula. Consequently, a stab wound was made in the posterior

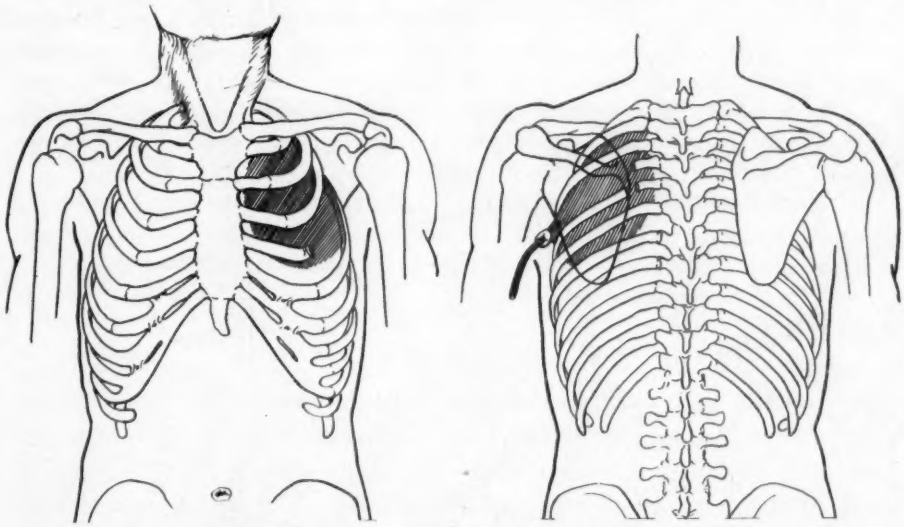

Fig. 5 (Case 2).—Representation of the surgical procedure involved in marsupialization of a hemorrhagic cyst of the left lung.

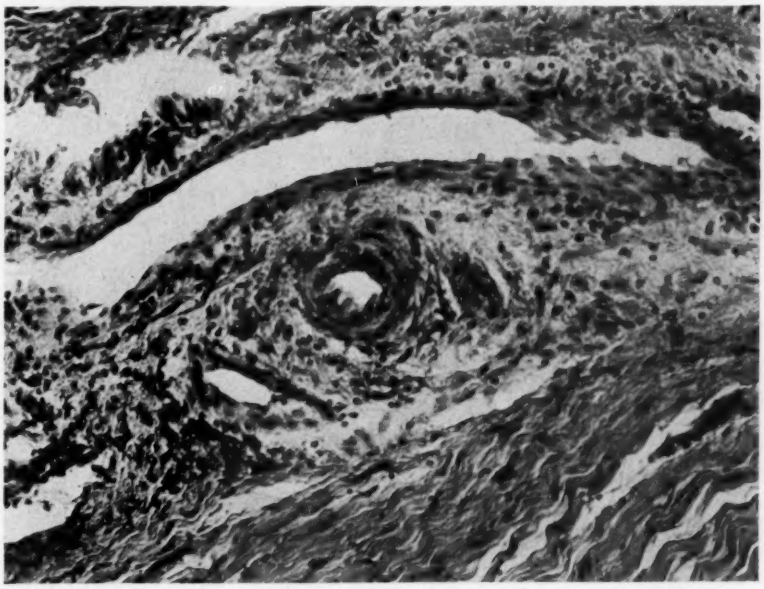

Fig. 6 (Case 2).—Section of the wall of a hemorrhagic cyst of the lung; the predominant feature is the fibrous tissue; inflammatory cells are evident around the vessels (hematoxylin and eosin ×160).

axillary line overlying the lateral portion of the fourth rib, which had been removed from the angle to this particular point (Fig. 5). The cystic structure was then opened, and a large quantity of old, black, clotted blood was removed. An opening approximately 3 cm. in length was made and the edges were brought up to the

deep fascia in the region of the stab wound. In this way, direct communication was established into the cystic structure laterally and anatomic closure of the original incision was made without drainage. Three large Penrose drains were left in the depths of the cavity of the cyst and a small portion of the edge of the cystic cavity was removed and sent to the laboratory for microscopic examination. The pathologists reported the cyst wall to contain fibrous and fatty inflammatory tissue (Fig. 6). Culture of the contents of the lung cyst (brain broth was used as a medium) revealed no growth of organism, nor were organisms grown on blood agar. Carbolfuchsin stain of a smeared specimen revealed no acid-fast bacilli.

The patient withstood the operative procedure well. On the eleventh postoperative day he was allowed to sit in a chair for limited periods daily; he was afebrile and his general condition was excellent. Large quantities of black blood clot drained from the marsupialized region.

COMMENT

These cases were doubly interesting to us because it was impossible to make a correct diagnosis without the performance of thoracotomy and because of the unusual nature of the pathologic lesions found. In retrospect, it seems likely that the sudden shock and dyspnea experienced by the first patient represented extensive hemorrhage into the cystic cavities. He had had hemoptysis on only one occasion. The bronchi communicating with the cystic cavities must have become occluded and remained so until late in the patient's postoperative course. Hennell reported on a patient in whom a cyst containing blood was found at necropsy. Harrington[6] was able to remove in its entirety a cyst filled with blood. Although these are the only such cases of blood-filled cysts with which we are familiar, it would seem that such a complication would be a frequent one, the frequency of hemoptysis among patients who have such cysts being indicative of the delicacy of the vessels of the wall of the cyst. The bronchi leading to the cyst frequently are distorted and tortuous, so that it is not surprising that in the cases reported herein they should have become occluded and failed to drain the cyst properly.

In the cases presented herein, it was hoped that by marsupialization of the walls of the two cysts the uninvolved portion of the left lung could be made to re-expand and obliterate the cystic cavities.

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PARAVERTEBRAL THORACOPLASTY FOR THE TREATMENT OF PULMONARY TUBERCULOSIS

A Report of 146 Cases With Follow-Up

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THE object of this paper is to review the material which has been made available from the treatment of 146 cases of pulmonary tuberculosis by paravertebral thoracoplasty. This series consists of all patients operated upon by this method at Grasslands Hospital from February, 1932, through July, 1940. A complete follow-up is reported on all but three cases within the past six months. All three not followed were classified as arrested when last heard from.

The procedures used to obtain collapse of pulmonary tissue by surgical means are less than thirty years old. Over these years marked improvement in technique has resulted in a lowering of the mortality rate and an increase in the number of cures. This is especially true during the last ten years in which the most rapid advances have been made. It can be said that certain factors, entering into selection of cases suitable for operation and having to deal with the treatment, are now more or less agreed upon as uniform.

When this work was first undertaken, the selection of cases for thoracoplasty was accomplished by rather conventional requirements, but during the years this has been tempered by experience. In the Tuberculosis Division of Grasslands Hospital, comprising 275 adult beds, the number of cases of advanced disease is high, as in any similar institution, upwards of 90 per cent. In the advanced disease group the basis for operative selection undoubtedly has been broadened, thereby giving certain cases a chance for surgical cure which might otherwise have been considered too far progressed for operation. In the main, we have insisted on adequate previous medical regimen, including minor collapse measures and evidence of productive changes. We have been rather liberal in evaluating contralateral involvement, laryngeal and intestinal disease, and upper age limit as contraindications for operation.

Each patient must have a satisfactory blood count and hemoglobin level and, if necessary, blood transfusions are given to bring these up to normal. We prefer to start the operation at a time when the patient is gaining weight, certainly when there has been no recent serious loss.

For several years we conscientiously carried out vital capacity, circulation time, and venous pressure determinations, believing that a more accurate estimate of the patient's ability to withstand the operative procedure could be arrived at. Vital capacity determinations have been

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Received for publication, Aug. 29, 1941.

more or less in vogue for periods of a few years since about 1850. Its popularity has vacillated but it has been revived, from time to time, by hopeful workers in the field of respiratory diseases, especially with the development of new surgical procedures, in which the test was thought to have prognostic bearing. During the 1920's, when thoracoplasty became a more frequently used operation, the test again sprang into prominence. During the past few years doubt has again arisen as to its real value and its limitations emphasized. This has resulted in more refined methods of functional cardiorespiratory determinations. Many clinics, including our own, are now encouraging more careful studies into functional respiratory reserve for patients considered for thoracoplasty. We are encouraged by the information provided by bronchospirometry and are equipping our clinic with apparatus for detailed studies by Dr. William A. Zavod.

Because of the numerous factors involved in the determination of vital capacity, such as loss or gain in weight, cardiac disease, fluid or air in the chest cavity, the effects of phrenic nerve interruption and emphysema, the accuracy of this test as a guide may be unreliable. Given two patients with similar clinical and x-ray findings, one often finds wide variations in the anticipated respiratory reserve. We still use the test because it does provide some information. We feel that the lower limit of vital capacity should be 40 per cent. However, if after removal of ribs it is thought that there will not be a harmful decrease in the amount of good lung tissue, then we do not hesitate to proceed with a vital capacity of less. But, in general, patients with a reading of less than 40 per cent are apt to do poorly. The test is repeated after each stage of the operation.

In evaluating the results of venous pressure estimations before operation and between stages, we found no great variations in the readings. If it was observed that the venous pressure was high after any given stage, we were inclined to wait a longer interval before proceeding with the next operation, as emphasized by Overholt and Pilcher.[1] During the past two years the test has not been done routinely because the results apparently did not justify its use.

For several years the circulation time was determined. This has also been abandoned as we came to the conclusion that no valuable help was obtained in evaluating the surgical risk. We have depended, to a large extent, on clinical judgment and experience to estimate this part of the patient's share in the prognosis.

In general, the contraindications to operation are advanced contralateral disease, advanced intestinal and renal disease, lack of inherent ability to form fibrosis or inadequate functional reserve.

Generally speaking, patients operated upon by us fall into groups of favorable, doubtful, and poor risks. We have come to the conclusion that the following factors make up the three grades for evaluation of the risk:

Grade I

a. Under 40 years of age
b. Localized disease, stationary lesion
c. Afebrile
d. Gaining weight
e. Adequate functional reserve
f. Normal blood pressure
g. Minimal concurrent disease

Grade II

a. Upper age group
b. Stationary or slightly progressive lesion
c. Contralateral disease which is stationary
d. Moderate functional reserve
e. Controlled empyema
f. Without bronchopleural fistula
g. Mild concurrent tuberculous disease

Group III

a. Upper age limit
b. Acute lesion of any type
c. Contralateral progressive disease
d. Bronchopleural fistula
e. Hypertension
f. Extensive concurrent tuberculous disease
g. Extensive fibrosis and emphysema with low functional reserve.

Alexander[2] has pointed out the disadvantages of such a classification, and on the whole, we agree with him, but when faced with such a large group of advanced cases, where the outlook is not always good, we feel justified in gauging our prognosis with established facts.

In accordance with this classification, we find: favorable, 76; doubtful, 41; poor, 29.

Racial analysis reveals that there were 119 patients of the white race, 1 of the yellow race, and 26 negroes.

Table I shows the series according to age and sex.

TABLE I

THORACOPLASTIES BY AGE AND SEX

AGE	MALE	FEMALE	TOTAL
11-20 yr.	2	5	7
21-30 yr.	27	31	58
31-40 yr.	30	13	43
41-50 yr.	19	11	30
51-60 yr.	7	1	8
	85	61	146

The average length of treatment prior to operation for the series was about two years. Pneumothorax had proved to be an operative or therapeutic failure in all cases. Phrenic nerve operations were performed on 31 of the patients before thoracoplasty and on 2 after operation.

The role played by phrenic nerve paralysis as an aid in major collapse is, in our experience, a minor one. We formerly used permanent interruption of the nerve for numerous accepted indications which, in the course of time, proved to be of questionable value and hence died a slow but certain death. Temporary nerve paralysis still has a place but its indications have decreased and it is now used by us mainly to control hemorrhage or to give mechanical advantage to pneumothorax. Phrenic exeresis has never been done by us, the procedure being considered too hazardous. We believe that a functioning diaphragm will aid in clearing secretions from the lower lobes and maintain to a certain extent a more adequate function of the air-containing tissue in the uncollapsed portion of the lung.

In this series, preceding thoracoplasty, closed pneumonolysis was done in 23 instances and open pneumonolysis in 1. Extrapleural pneumothorax was done in 5 cases, in 2 instances in preparation for thoracoplasty. In 3 cases the procedure alone proved to be a therapeutic failure. Apicolysis was done in 4 of the series and oleothorax in 4. Pneumoperitoneum has been tried in 6 cases.

Cavity size varied from 2 to 16 cm., the average for the entire group being 5.4 cm. Cavities were located on the right side in 77 and on the left in 69 instances.

Forty-six of the patients receiving thoracoplasty had clear fluid in the pleural space, usually complicating pneumothorax. Twenty-seven had frank tuberculous empyema, 11 of whom had shown a mixed pyogenic infection at one time or another. In 7 of these bronchopleural fistulas were known to be present.

Anesthesia, in the early days, was somewhat of a problem, but never a serious one, because the anesthetic staff at Grasslands Hospital has been uniformly capable during the years. We have passed through the local anesthesia phase, through the avertin gas and oxygen combination, the spinal for lower stages, the evipal plus cyclopropane, and finally adopting the cyclopropane with the intratracheal tube as the most satisfactory, from the patient's as well as the surgeon's standpoint. The position of the patient on the table is such that the head is lower than the chest, the head of the table being turned down about 15 degrees from the horizontal. This allows easy removal of secretions from the trachea through aspiration by the anesthetist or escape from the mouth after gravitation to the pharynx.

Three hundred and twenty-three staged operations were done and 15 patients had, in addition, one or more supplementary operations.

When this series was started in 1932, the operation was frequently done from below up. The complete thoracoplasty was always done in three stages or more. We prefer to wait about four weeks between stages, this period being determined by the patient's reaction and x-ray findings from films made about three or four weeks after any given

stage. In 3 instances, an unusually long time between stages elapsed because of contralateral spread, hemorrhage, and unfavorable postoperative recovery.

The first partial thoracoplasty in this series was done in 1932 in two stages, and since 1934 the two-stage six or seven rib thoracoplasty from above down has predominated. The complete operation has been done only eighteen times in the past four years.

In 1936 we began to use extrafascial apicolysis as recommended by Semb.[3] Since then it has been used in every case where indicated. It is our feeling that more cavity closures have been obtained by use of this adjunct. The cavities, instead of being compressed from above down against the mediastinum, appear to change their shape before closure as though the pressure were being applied from behind, laterally and above. Mobilization of the apex, especially in the posterior gutter, allows the lobe to be pushed more anteriorly. This procedure lengthens the time of operation ten to twenty minutes, and requires a careful dissection to avoid injury to the nerves and the subclavian vein. We have had no injury to the subclavian vein, one minor injury to the ulnar division of the brachial plexus, as evidenced by pain for three months in the forearm and hand, and one case of sympathetic nerve disturbance. In several patients, directly after apicolysis, we have observed a rise in temperature to 102 or 103°, symptoms of toxicity, and a decrease in expectoration. We have regarded this as caused by an obstruction to drainage of the cavity. This state persists for a few days and promptly subsides when the contents of the obstructed cavity are evacuated. We do not feel that the ultimate closure of the cavity is affected by this episode.

The complications encountered soon after operation were, in the main, spread of the disease locally or in the contralateral lung, pulmonary hemorrhage, severe dyspnea, and cardiac embarrassment. We have not seen a single case of meningitis or brain abscess as a complication. One patient developed a popliteal embolus which required subsequent amputation of the leg. Infection of the wound in this group of approximately 300 operations occurred as follows: 8 massive, 5 moderate, and 10 mild. In 4 cases chronic discharging sinuses persisted. All the infections were eventually controlled and no death was attributable to wound infection.

The late complications were chiefly progressive disease, reopening of bronchopleural fistulas, and in one case, development of a bronchopleural cutaneous fistula. Osteomyelitis of the ribs has occurred infrequently and has not persisted as a complicating factor.

There is less cervical spinal deformity if the transverse processes of the first three vertebrae are left long.

After surgery we prefer to keep the patients on strict bed rest until the sputum has been repeatedly negative for a period of three to six

months and general improvement is in evidence. The patients are then placed on graduated exercise until one hour's walking exercise twice a day or its equivalent is reached and improvement is such that the patient can be discharged as arrested. After discharge the patients are returned to clinic for examination every three months during the first year and thereafter every six months or as indicated. All follow-up examinations include x-ray of the lungs and concentrated sputum examination, in addition to the routine interval history and physical examination. Culture or guinea pig studies are now being done when sputum conversion is reported on concentration.

Of the 146 patients operated upon, 100, or 68.4 per cent, are living and 46, or 31.6 per cent, are dead from all causes. These deaths have occurred in a postoperative period ranging from one to eight years.

Table II gives the analysis of results of thoracoplasty.

TABLE II

RESULTS OBTAINED IN 146 PATIENTS

Arrested		93 (63.7%)
Living	85	
Dead from other causes than tuberculosis or operation	8	
Improved		7 (4.8%)
Unimproved		8 (5.4%)
Dead		46 (31.5%)
Operative	12 (8.2%)	
Progressive disease	25 (17.1%)	
Other causes	9 (6.2%)	

An analysis of the deaths according to age and sex is shown in Table III.

TABLE III

DEATHS ACCORDING TO AGE AND SEX

AGE	MALE	FEMALE	TOTAL	NO. OF OPERATIONS
11-20 yr.	0	2	2	5
21-30 yr.	7	8	15	56
31-40 yr.	9	3	12	41
41-50 yr.	10	4	14	31
51-60 yr.	3	0	3	10
	29	17	46	143

Table IV gives the results by selective groups:

TABLE IV

DEATHS ACCORDING TO RISK
(ALL CAUSES, ONE TO EIGHT YEARS)

Favorable		76
Dead	3 (3.9%)	
Doubtful		41
Dead	20 (48.8%)	
Poor		29
Dead	23 (79.3%)	

The observations made on this group of patients are especially valuable, in our opinion, because of the almost complete follow-up. Only

3 patients have not been heard from during the last six months and all of these were classified as arrested when last reported. Of the remaining patients, all but 22 were examined by us. The others responded to questionnaire.

The 9 deaths due to causes other than tuberculosis were: suicide (1); this patient was depressed because we were unable to proceed with the second stage, due to spread of the disease; nontuberculous nephritis (1), three years after closed cavity and negative sputum; involutional melancholia (1), six months after negative sputum; nontuberculous pneumonia (1), one year after negative sputum; lymphosarcoma (1), two years after a successful result. One death occurred in a white male, aged 44 years, with arrested disease for two years, who suddenly developed weakness in the lower extremities, with loss of sphincter control of the urinary bladder. A clinical diagnosis of transverse myelitis was made. He failed rapidly and expired seven days later. An autopsy revealed healed pulmonary tuberculosis. There was considerable emphysema and arteriosclerosis and a liver weighing 1,575 Grams, which revealed a hematoma 1 cm. in diameter and extending to about ¾ to 1 cm. below the capsule. No other cause of death was stated. Two patients died of cardiac decompensation (post mortem on both), one five years after the disease was arrested and the other two years. The other patient was seen in the psychiatric division of this hospital only a few weeks before death and his tuberculosis was arrested at that time. The patient was released from the hospital with a diagnosis of paranoid schizophrenia and died shortly afterward at home.

Twelve deaths (8.2 per cent) occurred within the first ten days after operation. These have been classified as operative deaths, but it is highly questionable if operation alone was responsible. In 3 of these cases, the patients died of massive pulmonary hemorrhage, 1 following the first stage and 2 following the second stage. Five deaths in this group occurred in patients who, from general and x-ray appearance seemed at the time to be good risks, although because of low vital capacity, fall into the doubtful group. All had chronic disease with emphysema and 4 had a vital capacity of less than 40 per cent. Post-mortem examination was obtained in 2 of these 5 patients and no other cause of death could be found. They all had dyspnea and cyanosis following operation. One of the 12 died of acute cardiac dilatation, proved by post-mortem examination. The other 3 deaths in this group were attributed to postoperative shock.

Twenty-five of the deaths were due to progressive pulmonary and pleural disease. One of these patients was considered an arrested case but was readmitted two years later with recurrent pulmonary hemorrhage, from which he eventually died, although the sputum was negative and at post-mortem examination the original cavity was described as healed. However, there was extensive bronchiectasis beneath the thoracoplasty, giving rise to hemorrhage.

Nine of the cases originally presented caseous pneumonic lesions where pneumothorax had been attempted and abandoned because of failure. Seven were in negroes, and two in whites, all complicated by empyema and 3 having proved bronchopleural fistulas. In another case, the sputum had been negative for eight years, but thin bloody fluid continued to build up beneath the thoracoplasty, necessitating repeated aspirations. A bronchopleural fistula suddenly developed and the fluid became secondarily infected necessitating open drainage. The patient died in seven months from spread of the tuberculous disease. Another patient died of extensive amyloidosis five years after a negative sputum. On post-mortem examination no active tuberculosis was found and a healed cavity was described, but there was a large loculated empyema pocket in the posterior gutter, filled with thick tuberculous pus. The other 13 patients died of progressive tuberculosis and in all instances the contralateral lung was extensively involved.

It is interesting to note that healing of cavity was described in 3 of the post-mortem examinations.

All of our patients were classified as far advanced. Most of these were chronic cases previously receiving long sanatorium treatment without improvement and in whom treatment would have been prolonged. This is illustrated in the case of a patient who had received nine years of sanatorium treatment and who was discharged one year and four months after surgery was completed.

All patients classified as arrested and who have been followed in our clinic are in excellent condition. There is some degree of scoliosis present in all patients graded by us as severe in 8, moderate in 10, and slight in the others, but is not incapacitating in any instance. The majority of these arrested cases are employed in some gainful occupation. As regards function, meaning good arm motion and adequate vital capacity, there are 88 good, 11 fair, and 1 poor result. Deformity from a purely aesthetic point of view revealed 89 good, 14 fair, and 6 poor.

Our results show that 68.5 per cent of our patients were improved and of this group 63.7 per cent were classified as arrested, or apparently cured, after being subjected to rigid examination. These figures compare favorably with those of Freedlander and Wolpaw,[4] who reported 57 per cent negative sputum cases and 9 per cent improved, or a total of 66 per cent improved out of a series of 85 cases. They also compare favorably with those of Overholt,[5] Maurer and de Savitsch,[6] and Coryllos[7] all of whom report approximately 70 per cent of the operated cases improved but do not, however, mention the number of cases in which there has been permanent sputum conversion. Wangensteen, Carlson, and Bowers,[8] in a series of 42 cases, reported 50 per cent with negative sputum and a total of 71.5 per cent improved. Our figures show definite improvement over those collected from the literature by Dolley, Jones, and Paxton,[9] representing a total of 636 cases

with only 43 per cent improved. No doubt this is due to improvement in selection and technique.

Of our improved group, all are able to do part- or full-time work but are handicapped by recurrent positive sputum or slight pulmonary changes evidenced by x-ray and elevation of temperature and malaise from time to time.

We believe that poor results from thoracoplasty can be expected in chronic cases with emphysema and fibrosis, where there is limited functional reserve. Better selection in this group can be made by careful respiratory functional determinations before operation as described by Richards and Cournand.[10] Especially hazardous, in our limited experience, are the acute lesions temporarily controlled with pneumothorax, when complicated by empyema and particularly if bronchopleural fistulas are present.

Undoubtedly other complications, such as systemic disease, extent of involvement, protracted multiform tuberculosis, and age influence results, but these are not factors of special interest in this series.

SUMMARY

1. One hundred forty-six cases of paravertebral thoracoplasty for the treatment of pulmonary tuberculosis are reported.

2. Complete follow-up was obtained on all but 3 patients, who were classified as arrested when last heard from.

3. Improvement occurred in 68.5 per cent and of these 93 or 63.7 per cent, by critical analysis were arrested or apparently cured.

4. Forty-six, or 31.5 per cent, of the patients are dead from all causes during one to eight years. Twelve, or 8.2 per cent, are listed as operative deaths; 9, or 6.2 per cent, died of causes other than tuberculosis; and the remaining 25, or 17.1 per cent, died of progressive tuberculous disease.

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THE SURGICAL TREATMENT OF LARGE CARBUNCLES IN DIABETIC AND NONDIABETIC INDIVIDUALS

With a Report of Twenty Cases

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FEW lesions are encountered more frequently in surgical practice than are ordinary furuncles. Excepting those developing on the face, they attract little attention from the surgeon. The vast majority of these minor infections respond to a wide variety of therapeutic measures, resulting eventually in complete cure. The fact that furuncles rank high among the causes of disability in industry, producing their full share of pain to the unfortunate patient, is all too frequently overlooked.

In contrast to these simple infections, a true carbuncle with extensive involvement of the subcutaneous tissue and multiple draining sinuses through the overlying skin presents a surgical problem of major importance. The seriousness of these lesions is further increased since they so frequently develop in older individuals with diabetes, nephritis, or other debilitating disease.

During the past few years we have observed a series of twenty patients with carbuncles of major size, necessitating hospitalization for treatment. For the purpose of this study all cases have been excluded which presented with small carbuncles suitable for treatment in the outpatient department or in office practice.

Several methods of treatment were used in the management of these twenty patients and this is quite in keeping with the highly divergent opinions expressed in the surgical literature. An analysis of our cases was therefore undertaken, together with a review of the experience of others, to more critically evaluate the therapeutic results obtained in the treatment of these lesions.

REPORT OF CASES

In any series of cases of large carbuncles it is essential that those developing in nondiabetic patients be considered apart from those in diabetics. The fulminating character of the diabetic carbuncle with its high attendant mortality presents a surgical problem of major importance and demands that this group of patients be considered separately.

(a) Carbuncles in nondiabetic patients.

There were thirteen patients in this group, of whom eight were females and five males. The average age was forty-five years. The most common site was the neck and shoulders, followed in order by the face, buttocks, and thighs. The average duration of the lesion on admission was thirteen days, the longest period being six weeks and the shortest two

Received for publication, Aug. 6, 1941.

TABLE I

CARBUNCLES IN NONDIABETIC PATIENTS

CASE	SEX	AGE	SIZE	SITE DURATION	TREATMENT				RESULT		HOSPITAL DAYS	COMMENT
					CONSERVATIVE	X-RAY	X-RAY AND SURGERY	SURGERY	RECOVERED	DIED		
1	F	25	4 cm.	Buttocks 6 days				Cruciate	Yes		2	Healed 2 wk.
2	F	63	15 cm.	Back 3 wk.				Cruciate	Yes		38	Skin graft; healed 8 wk.
3	F	41	9 cm.	Buttocks 1 wk.				Cruciate	Yes		7	Healed 6 wk.
4	F	45	18 cm.	Neck 2 wk.				Cruciate	Yes		28	Skin graft; healed 6 wk.
5	F	76	8 cm.	Back 2 wk.				Cruciate	Yes		8	Grafts not necessary
6	F	20	3 cm.	Hand 2 days				Cruciate	Yes		4	Healed 2 wk.
7	M	74	10 by 8 cm.	Shoulder 6 wk.			× Cruciate		Yes		32	Mental changes; x-ray not given thorough trial
8	M	67	20 by 20 cm.	Neck 4 wk.			× Cruciate			Yes	70	Patient dismissed improved; fatal endocarditis 2 mo.
9	M	34	8 cm.	Thigh 1 wk.				Cruciate	Yes		10	Practically healed on dismissal
10	M	60	11 by 7 cm.	Neck 4 wk.				Cruciate 2×	Yes		30	Two operations done; healed 7 wk.
11	F	25	3.5 cm.	Lip 3 days	×				Yes		7	Spontaneous drainage with x-ray and hot packs
12	F	40	3 cm.	Nose 3 days	×				Yes		5	Spontaneous drainage with hot packs
13	M	18	3 cm.	Lip 4 days	×				Yes		8	Spontaneous drainage with x-ray and hot packs

days. In size these carbuncles varied from 3 to 20 cm. in diameter, the smaller lesions being those on the lips and face, while the very extensive ones were those on the neck and shoulders. The therapy employed is tabulated in Table I.

Carbuncles on the face were treated entirely by conservative measures which included bed rest, continuous moist boric applications, and x-ray therapy in certain instances. Incision was employed in these cases only when it became necessary to drain a well-localized abscess.

Carbuncles appearing in other areas than the face were all treated by cruciate incision with undercutting of the skin flaps. In two very extensive cases x-ray was used in conjunction with wide incision as a pre- and postoperative adjunct. It was necessary to operate on one patient a second time because of further local extension of the infection. The average period of hospitalization for the group was nineteen days. Skin grafts were necessary in two cases but the remaining wounds healed without grafting in an average period of six weeks. There was only one death in this group of patients, resulting from septicemia and endocarditis. This man, aged sixty-seven years, with a very extensive carbuncle of his neck, made a good surgical recovery after cruciate incision and the subsequent application of split grafts. He was dismissed from the hospital with his wound almost healed. Two months later he was readmitted after an illness of two weeks. He was found to have a *Staphylococcus aureus* septicemia and post-mortem examination disclosed an acute vegetative endocarditis. There seems little doubt that this man's fatal illness resulted from a late complication of the original carbuncle.

(b) Carbuncles in diabetic patients.

This group of seven patients averaged fifty-six years of age and six occurred in males (Table II). Two of the seven were unaware that they had diabetes prior to admission while the remaining five were known diabetics for periods ranging from six months to thirty years. None of this latter group of known diabetics had been under proper medical management before the onset of their present illness. Six of the seven were definitely overweight, averaging 182 pounds.

These seven patients were all acutely ill on admission, with marked pain, fever, and prostration. A leucocytosis was present in every instance, averaging 20,000 cells per cubic millimeter for the group. In those cases in which blood smears were made, there was a striking shift to the left in the polymorphonuclear series, the stab cell counts averaging 22 per cent. These seven patients with diabetes responded in the usual manner when infection became established. In every case the diabetes became uncontrolled in spite of large and increasing insulin dosage, adequate drainage being the only means of bringing the altered metabolism into abeyance. One of these patients was treated entirely

TABLE II

DIABETIC PATIENTS WITH MAJOR CARBUNCLES

CLINICAL DATA

CASE	SEX	AGE WEIGHT	KNOWN DIABETIC	SITE LESION	SIZE	DURATION	TEMPERATURE ADMISSION	W. B. C.	DAILY INSULIN	ORGANISM
1	M	62 200	Yes 30 yr.	Nose	3 cm.	3 days	101°	16,000	60 units not controlled	*Staph. aureus*
2	M	34 107	Yes 6 mo.	Cheek	3 cm.	10 days	99.4°	6,700 19% stab cells	60 units not controlled	Nonhemolytic streptococcus
3	M	72 165	Yes 5 days	Neck	12 by 6 cm.	17 days	101°	12,600 48% stab cells	60 units not controlled	Nonhemolytic streptococcus
4	M	64 184	Yes 3 yr.	Neck	8 by 10 cm.	10 days	100°	16,200 2% stab cells	60 units not controlled	*Staph. aureus*
5	M	44 204	Yes 5 days	Neck	16 by 18 cm.	2 wk.	101.4°	30,800 36% stab cells	200 units not controlled	Hemolytic *Staph. aureus*
6	F	57 160	Yes 17 yr.	Neck	6 by 8 cm.	3 wk.	101°	32,000 24% stab cells	90 units not controlled	*Staph. aureus*
7	M	63 180	Yes 10 mo.	Neck	12 by 12 cm.	10 days	100.8°	26,100 5% stab cells	75 units not controlled	Not cultured

by conservative means, one by cruciate incision alone, and the remaining five by x-ray therapy, and surgical drainage. Surgical excision was carried out in one of these five patients, cruciate incision being employed in the other four. Extension of the inflammatory process necessitated secondary operations in two patients (Table III). Sulfathiazole

TABLE III

DIABETIC PATIENTS WITH MAJOR CARBUNCLES

TREATMENT AND RESULTS

CASE	TREATMENT				RESULTS		HOSPITAL DAYS	CAUSE OF DEATH	COMMENT
	X-RAY	X-RAY AND SURGERY	SURGERY ALONE	CONSERVATIVE	RECOVERED	DIED			
1		Yes Incision			Yes		21		Opened when well localized
2				Yes	Yes		36		Spontaneous drainage
3			Cruciate			Yes	4	Septicemia	Uncontrolled diabetic; no response to therapy; sepsis and pyemia
4		Yes Cruciate			Yes		46		X-ray for 6 days; diabetes not controlled; lesion unchanged; response to surgery
5		Yes Cruciate 2 operations				Yes	31	No post mortem	Terminal leucopenia; possibly sulfathiazole effect
6		Yes Cruciate			Yes		66		X-ray 9 days; lesion unchanged; diabetes not controlled; response to surgery
7		Yes 3 operations X-ray Transfusion				Yes	32	Sepsis	Severe diabetic; no previous control; surgery too conservative at outset; no resistance

in large doses was used as an adjunct to x-ray and surgery in two patients, transfusion also being employed in the same individuals.

There were three deaths in this small series of diabetic patients, resulting in a mortality of 42.8 per cent for the group.

CASE 1.—An obese male, 72 years of age, was acutely ill on admission to the University Hospital, with a temperature of 101° F. A carbuncle of the neck, 12 × 6 cm. in diameter, had been present for seventeen days. Diabetes was discovered on admission to hospital. Treatment consisted of wide cruciate incision together with diabetic care. The diabetes remained uncontrolled and the patient made no response to treatment. Death occurred from septicemia four days after admission. A nonhemolytic streptococcus was demonstrated on blood culture. No post-mortem permitted.

CASE 2.—An obese male, 44 years of age, was admitted to the University Hospital acutely ill with a temperature of 101.4° F. An extensive carbuncle of the neck, measuring 16 × 18 cm., had been present for two weeks. Diabetes was discovered for the first time five days prior to admission. Treatment consisted of wide cruciate incision and the incision was enlarged on two occasions because of extension of the lesion. X-ray therapy and large doses of sulfathiazole were also employed. The diabetes, which was at first uncontrollable in spite of 200 units of insulin per day, became regulated when adequate surgical drainage was obtained. Recovery seemed assured and the wound was healing satisfactorily when the patient suddenly became listless, apathetic, and irrational. A leucopenia developed with complete agranulocytosis. Death occurred on the thirty-first hospital day, ninety hours after the onset of this complication. A blood culture on the last day of life was negative. A post-mortem was not permitted. The clinical impression was that death probably resulted from agranulocytosis incident to sulfathiazole.

CASE 3.—An obese male, 64 years of age, was admitted to the Methodist Hospital with a temperature of 100.8° F. A carbuncle of the neck, 12 × 12 cm., had been present for a period of ten days. The patient was a known diabetic of ten months' duration but had not been under adequate medical control. Cruciate incision, without undercutting, was carried out on two occasions but in neither instance was the entire area widely opened. Sulfathiazole was given in large doses, x-ray therapy was given daily, and the patient received two transfusions. The inflammatory process continued to advance, sepsis became more marked, and the diabetes was uncontrolled on 75 units of insulin per day. The patient was seen in consultation and more adequate surgical drainage was advised. Wide cruciate incision with complete undercutting of the flaps was carried out under pentothal sodium anesthesia. Temporary improvement was noted but pulmonary signs developed and death occurred on the thirty-second hospital day. No post-mortem was permitted. It would appear that the initial treatment in this case was too conservative with resultant loss of strength and resistance. It seems possible that more adequate surgical drainage at an earlier date might have altered the ultimate result.

DISCUSSION

The principal methods of treatment employed in the treatment of major carbuncles may be considered under four headings.

1. Conservative measures in which rest, hot packs, and x-ray therapy are the principal therapeutic agents.
2. X-ray therapy in conjunction with surgical drainage.
3. Early radical surgical drainage.
4. Miscellaneous methods.

(a) X-ray therapy. In Table IV several series of reported cases are summarized in which x-ray therapy was the principal method of treatment. Improved technique of radiation has resulted in providing a very valuable therapeutic agent with the principal advantages of prompt reduction in pain and a very satisfactory cosmetic result. Except in those cases in which treatment is begun very early, the period required for control of these lesions with x-ray is similar or only slightly less than that observed when surgery is employed. In the reported series of cases x-ray therapy alone has been adequate to effect a cure in from 60 to 90 per cent of the patients so treated, the percentage being higher

when therapy is started early. Surgical drainage becomes necessary to control the lesion in approximately 33 per cent of any group of patients receiving initial x-ray therapy. Hodges,[5] King,[3] Andrews,[6] and Light and Sosman,[1] all agree that the highest percentage of failures with x-ray therapy occurs in the treatment of deep carbuncles of the neck, and these authors all favor surgical incision for this type of lesion. In carbuncles of the blush area of the face x-ray therapy is now almost uniformly employed with an appreciable reduction in the mortality.

TABLE IV

X-RAY THERAPY IN THE TREATMENT OF MAJOR CARBUNCLES

AUTHOR	TOTAL NO. CASES	CASES X-RAY THERAPY ONLY	CASES AIDED %	CASES CURED %	CASES X-RAY FAILURE	CASES X-RAY FAILURE %	CASES X-RAY AND SURGERY	MORTALITY		COMMENT
								CASES	%	
Light and Sosman	50	34	66	60	16	32	16 33%	2	4	Failure in 40% lesions neck in men
Firor	56	38	70	66	1	1	18 33%	0	0	
King	39	36	70	66	3	33	3 8.3%	0	0	Surgery better for deep lesions of neck
Lewis	16	14		87.4	2	12.4	2 12.4%	0	0	
Hodges	26	24		92	2	8	2 8%	0	0	Advise surgery for deep neck lesions in men

(b) X-ray therapy in conjunction with surgical drainage is the most popular method of treatment employed today in the treatment of major carbuncles. In Table V several reported series of cases are summarized indicating the methods of therapy and results obtained by different surgeons. One may conclude that x-ray therapy is definitely worthy of a trial in the treatment of nondiabetic carbuncles, excepting those deep lesions on the neck. If evidence of improvement is not apparent after five days' therapy, radical surgical drainage is indicated.

In analyzing these cases one outstanding fact is apparent. Most nondiabetic patients with major carbuncles recover unless the individual develops a septicemia with multiple abscesses or an endocarditis. The mortality in the nondiabetic group averages approximately 3 per cent. In contrast, the diabetic patient with a major carbuncle has a very different prognosis. Our experience, which is supported by the observations of others, has led us to consider such a lesion as serious as a moist gangrenous limb in a diabetic patient. With the onset of infection, the carbohydrate metabolism invariably becomes refractory to medical therapy, and fails to respond with the employment of conservative surgical measures. The mortality in this group of patients ranges from 25 to 40 per cent in the reported series. These patients are usually

obese, often are unaware they have diabetes until their admission to the hospital, and frequently are hospitalized for treatment days or weeks after the development of the carbuncle. We agree with McKittrick and Root[12] that the logical method of treatment demands immediate control of the patient's ketosis and the prompt institution of adequate surgical drainage, providing the lesion is not on the face. Needless delay spent in futile attempts to control the patient's diabetes and limit the inflammatory process by conservative methods results in a lowering of resistance and higher mortality.

TABLE V

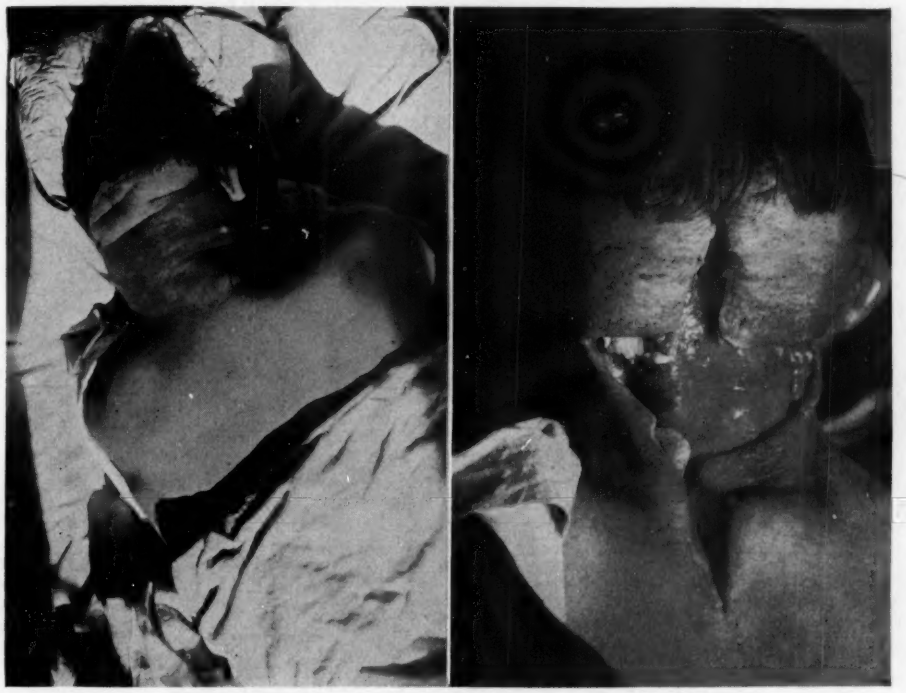
TREATMENT OF MAJOR CARBUNCLES

SUMMARY OF SEVERAL REPORTED SERIES

			MITCHINER	O'BRIEN	BERMAN	FALLIS AND HOOKER	CARP	MC KITTRICK AND ROOT	MCLAUGHLIN
	Total cases		240	130	125	166	153	19	20
	Diabetic cases		10	16	21	20	30	19	7
	% cases diabetic		2.4%	12.3%	16.8%	12%	19.6%	100%	35%
Therapy non-diabetic patients	Conservative		114		25	36	33		3
	X-ray only			60		13	22		
	X-ray and surgery			70		3			2
	Surgery only	Incision	40		33	84	56		7
		Excision	86		67	23			1
	Deaths	Cases	9	1	3	4	3		1
		%	3.5%	0.8%	2.9%	2.7%	2.5%		7.6%
Therapy patients with diabetes	Conservative		1				1		1
	X-ray only						6		
	X-ray and surgery								4
	Surgery only	Incision	4				23	19	2
		Excision	5						
	Deaths	Cases	4	4	6	5	8	5	3
		%	40%	25%	28.5%	25%	27%	26.3%	42.8%
Lesions Face	Cases		83	57		25			4
	Deaths		7	0		5			0
	% Deaths		8.4%	0%		20%			0%

(c) Radical surgical drainage is the method of choice when a decision has been made to employ surgery. One has only to recall the characteristic pathology of a carbuncle to realize the futility of obtaining adequate drainage by means of conservative or "medical" incisions. Complete excision of the lesion either with the actual cautery as advocated by Mowery[13] or the electric knife suggested by Jopson[14] has its adherents. Hosford[15] favors this method when feasible in all diabetic patients. These methods undoubtedly do remove the entire infected area but the resultant period of disability and scarring have not contributed to their popularity. Wide cruciate incisions extending completely across the entire area with complete undercutting of the flaps as practiced by Kanavel[16] is probably the most popular method of surgical drainage employed. More recently Livingston[17] has described a

double cruciate incision with sliding flaps, and Maes[18] a gridiron incision to provide drainage comparable to that produced by the usual cruciate incision with more rapid healing and a smaller scar. We have routinely employed a wide cruciate incision with undercutting of the skin flaps when surgical drainage was undertaken (Fig. 1). Zinc peroxide (Z.P.O.) is a very useful initial dressing for these wounds, followed in a few days by Dakin's solution to facilitate separation of adherent necrotic tissue. The skin flaps are approximated with flamed adhesive tape as soon as the base of the wound is covered with healthy granulation tissue. The resultant scar is usually much less noticeable than anticipated and skin grafts are only occasionally necessary (Fig. 2).



A. *B.*

Fig. 1.—*A*, Large carbuncle on back of neck in a diabetic patient of two weeks' duration. *B*, Appearance ten days after wide cruciate incision with undercutting of skin flaps. Healing was facilitated by approximating the skin flaps with flamed adhesive tape.

It must be constantly borne in mind that the inflammatory process may extend after the primary operation is carried out, necessitating further surgery. We have found this necessary on three occasions in our series of cases.

Practically all now agree that radical surgical methods have no place in the treatment of carbuncles of the upper lip and blush areas. Lilienthal[19] has recently suggested incision through the vermilion border of the upper lip for the treatment of carbuncles in this region but stresses

the danger of going through infected tissue. It is generally considered that surgical procedures in these regions should be limited to the removal of crusts or simple incision when necessary to release pus from well-localized and completely liquefied pockets. Ligation of the angular vein was advocated by Bailey,[20] in 1928, to prevent the development of cavernous sinus thrombosis, although it was admitted that this only represented one route of drainage from the blush area. More recently Batson[21] has demonstrated by injection experiments that ligation of the angular vein does not prevent septic emboli in the facial vein from

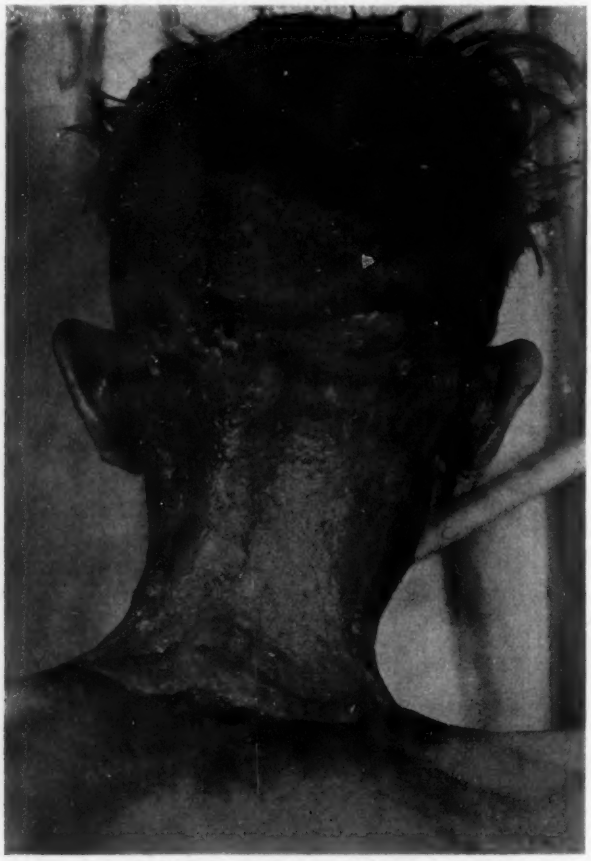


Fig. 2.—Late appearance of a very extensive carbuncle of the neck in a nondiabetic patient with destruction of skin through necrosis. Entire area subsequently covered with split grafts.

entering the cavernous sinus by several other routes. Fraser,[22] Gordon,[23] and Roberts,[24] have all pointed out the futility of this procedure and it is rarely employed today.

(d) A group of the less frequently employed methods used in the treatment of carbuncles are listed in Table VI. Of these, autohemotherapy as employed by Carp[28] and Dutt[29] has been sufficiently successful to warrant a more extensive clinical trial. Since the publication of Carp's paper in 1927, only one additional report of the use of autohemotherapy has appeared in the American or English literature.

TABLE VI

THERAPY OF CARBUNCLES

MISCELLANEOUS METHODS

AUTHOR	CASES	DIA-THERMY CAUTERY PUNCTURE	MAG-NESIUM SULFATE PASTE	AUTO-HEMO-INJEC-TIONS	SURGERY AND SULFONA-MIDES	RECOV-ERED	DIED	MOR-TALITY
Fellman	3	3				3	0	0%
Beling and Abel	13				13	13	0	0%
Morison	28		28			28	0	0%
Carp	12			12		12	0	0%
Dutt	8			8		8	0	0%
Brown	2			2		2	0	0%

We have had no personal experience with this method but through the courtesy of Dr. Alfred Brown the following two cases are reported in which it was successfully employed.

CASE 1.—Male, aged 38 years, was seen on June 9, 1927, with a large furuncle on the back of the neck, present for one week. Hot packs were applied but the following day the lesion was more extensive, having all the characteristics of a true carbuncle. The temperature was 99.4° F., the white blood count 17,400, urine negative. On June 17, 1927, 40 c.c. of whole blood were injected into four quadrants about and beneath the lesion. The following day pain was lessened considerably and there was no evidence of extension. The center of the lesion became soft and there was profuse purulent drainage. Following the initial autohemo-injection no further treatment was necessary excepting frequent dressings. Healing progressed rapidly and the patient was dismissed with the wound healed eighteen days after the autohemo-injection.

CASE 2.—Male, aged 39 years, was seen on November 15, 1928, with typical carbuncle on back of the neck present for period of four days. Urine negative. The patient was immediately admitted to the Clarkson Hospital where the entire periphery of the lesion was injected with autogenous whole blood under gas anesthesia. Pain was promptly relieved and the following day he left the hospital. The inflammatory area rapidly decreased in size and discharge from the center of the area diminished. The patient was dismissed five days after the autohemo-injection. Dressings were no longer necessary and healing was complete.

NOTE: We wish to express our appreciation to Dr. Alfred Brown for the privilege of including in this report his two cases successfully treated by autohemotherapy.

SUMMARY AND CONCLUSIONS

1. A series of twenty major carbuncles are reported, thirteen developing in nondiabetic and seven in diabetic patients.

2. The mortality in the nondiabetic patients should be low, death almost always resulting from septicemia with its attendant complications.

3. The mortality from large carbuncles developing in diabetic patients is high, ranging from 25 to 42 per cent in the reported series of cases.

4. Conservative measures, including x-ray therapy, should be employed in the treatment of all carbuncles on the face in both diabetic and nondiabetic patients. Ligation of the angular vein in these individuals is not warranted.

5. In nondiabetic carbuncles, excepting deep lesions on the neck, x-ray and conservative methods are worthy of a trial. If there is not definite improvement in a few days, wide cruciate incision with undercutting of the flaps is indicated.

6. Early radical surgery is the treatment of choice in all deep carbuncles of the neck.

7. Autohemotherapy is a method of therapy worthy of further clinical trial in the treatment of major carbuncles which are seen early.

8. Carbuncles in diabetic patients, excepting those on the face, do not respond well to conservative measures. Early radical surgery is indicated.

9. The value of the sulfonamides in the treatment of these lesions is not as yet determined.

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LOCALIZATION OF BISMUTH IN THE KIDNEY

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IT IS well known that bismuth compounds as used in the therapy of syphilis may be concentrated in the kidneys, and analyses carried out on experimental animals and on human beings have been reported from various laboratories.[1-5]

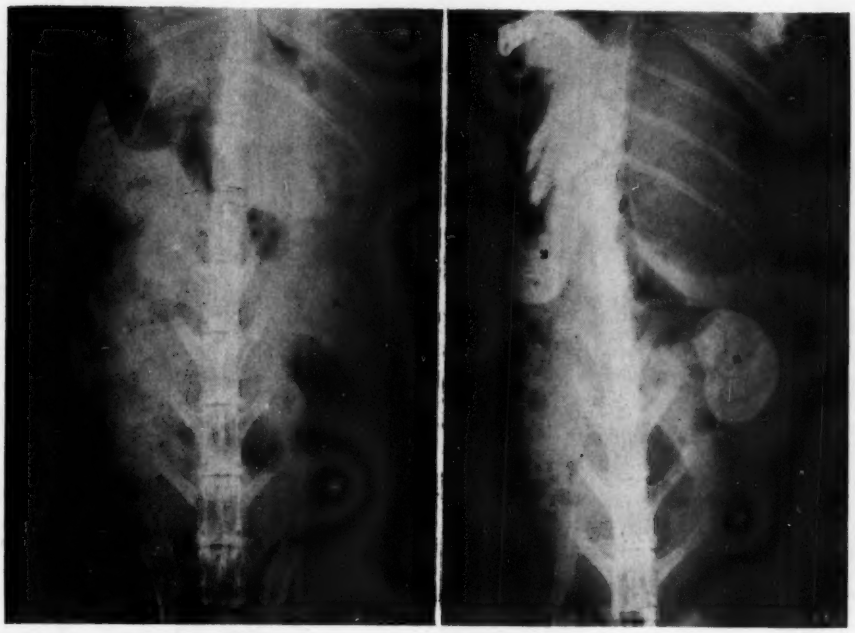
In our work on the localization of abscesses[6-8] we have also used the water-soluble bismuth compound thiobismol* (sodium bismuth thioglycollate). The experiments were conducted on brown Belgium rabbits who received varying amounts of thiobismol in one dose or in divided daily doses by intramuscular injection. Various organs were analyzed for bismuth contents by the method of Lehman, Richardson, and Hanzlik.[9]

The first group of rabbits were apparently normal animals from our stock. Control films of the kidneys were taken and then thiobismol in doses varying between 40 and 180 mg. was injected. Twenty-four hours after the last injection a roentgenogram was taken; in a number of animals films were taken after every injection. All films were taken with the animal on its back, and with the same focal distance, tube, and screen. In all six rabbits of this group a distinctly increased bismuth content was found in the kidneys as compared to other organs. In rabbits 5 and 6 (see Fig. 1) the substance of the kidney was found distinctly visible on the x-ray film twenty-four hours after the last injection of thiobismol. The kidneys of these rabbits contained relatively large amounts of calcium on chemical analysis. This observation may explain the visualization of one kidney in the control film of rabbit 6 (see Fig. 1). In rabbit 5 one kidney only appeared on the x-ray picture following the thiobismol injection, and autopsy revealed the presence of only one organ, a not quite infrequent observation in rabbits. In rabbits 1 to 4 the kidneys were not visualized.

The presence of large amounts of calcium salt in the kidneys of two rabbits indicated an abnormal condition of this organ which possibly was responsible for the accumulation of the bismuth. Therefore, in the next group of rabbits (7 to 10), an attempt was made to produce a pathologic condition of the kidney by the intravenous injection of 2 to 4 c.c. of ethylene glycol on subsequent days. Two days later thiobismol was injected and twenty-four hours after the last injection x-ray films

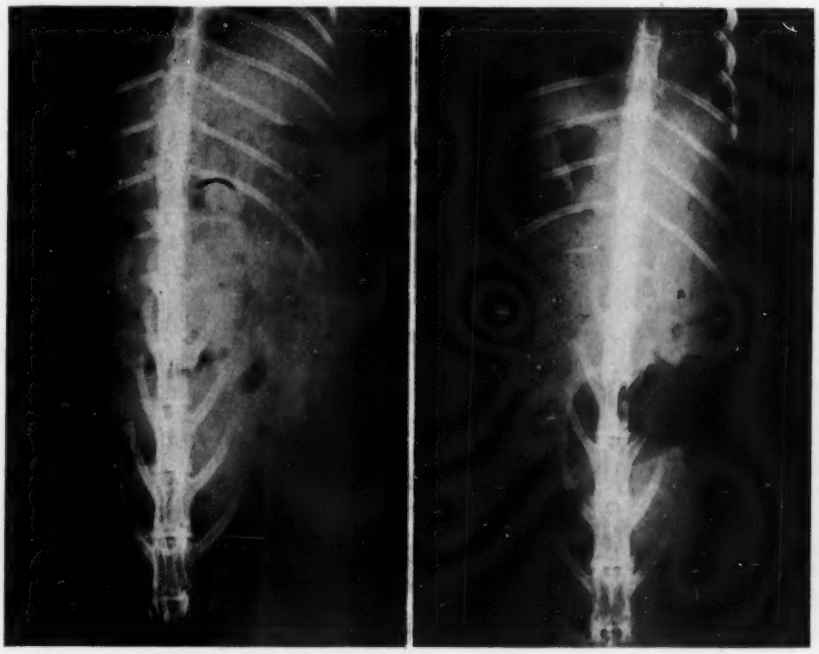
*Generously supplied by Dr. O. Kamm, Parke, Davis & Company,

Received for publication, Dec. 4, 1941.



A. *B.*

Fig. 1.—*A*, Rabbit No. 6, Table I, before injection of thiobismol. Faint shadow in left kidney. *B*, Rabbit No. 6, after injection of thiobismol. Distinct shadows in both kidneys.



A. *B.*

Fig. 2.—*A*, Rabbit No. 9, Table I, before injection of thiobismol. No shadow of kidneys. *B*, Rabbit No. 9, after injection of thiobismol. Distinct shadow of both kidneys.

TABLE I

LOCALIZATION OF BISMUTH IN THE KIDNEY

RABBIT NO.	C.C. ETHYLENE GLYCOL I. V.			X-RAY OF KIDNEYS	MG. THIOBISMOL I. M.			X-RAY OF KIDNEYS 24 HOURS AFTER LAST INJECTION	REMARKS
	NO. OF DAYS	INDIVIDUAL DOSE	TOTAL DOSE		NO. OF DAYS	INDIVIDUAL DOSE	TOTAL DOSE		
1				Negative	1	40	40	Negative	
2				Negative	12	15	180	Negative	
3				Negative	11	15	165	Negative	
4				Negative	11	15	165	Negative	
5				Negative	1	80	80	Distinct shadow, left kidney	No right kidney found at autopsy. Calcium in kidney
6				Faint shadow in left kidney	12	15	180	Distinct shadow, both kidneys (See Fig. 1)	Calcium in kidneys
7	2	4	8	Negative	8	15	120	Distinct shadow, both kidneys	
8	2	4	8	Negative	6	15	90	Distinct shadow, both kidneys	
9	2	2 and 4	6		6	15	90	Distinct shadow, both kidneys (See Fig. 2)	
10	2	4	8	Negative	8	15	120	Gas in intestines on all films. Visualization of kidneys doubtful	

were taken. In three of these four animals a distinct shadow of both kidneys was observed. Chemical analysis showed the presence of relatively large amounts of bismuth in the kidneys (see Fig. 2), but no significant amount of calcium was found. In the fourth rabbit (No. 10) repeated films gave inconclusive results, because large amounts of gas obscured the entire abdomen.

A histologic study of the kidneys of the animals treated with ethylene glycol and with ethylene glycol and thiobismol showed severe lesions of the glomeruli and tubules.*

SUMMARY AND CONCLUSIONS

Our experiments indicate that the kidney of the normal rabbit does not accumulate amounts of thiobismol sufficient for its visualization on the x-ray film. On the other hand, in rabbits with pre-existing kidney pathology, as evidenced by significant amounts of calcium in the kidneys, as well as in rabbits whose kidneys had been damaged by ethylene glycol, the injected thiobismol was accumulated by the diseased kidneys to such a degree that they acquired sufficient radiopaqueness to stand out very distinctly on the x-ray film.

It is known that the administration of thiobismol per se to the human being or animal can be followed by kidney damage,[10] and that the administration of this substance to patients with kidney disease is dangerous. We know from the studies of others that, in the human being and in animals, injected bismuth is excreted in the urine in large amounts,[11] and we had evidence of this in about half of our films by a dense bismuth shadow of the filled urinary bladder. We feel that our observations are worth-while reporting to give another warning against the use of thiobismol or similar compounds in the presence of damaged kidneys, and we want to draw the attention of the clinician to the possibility of demonstrating such conditions on the x-ray film. The production of radiopaqueness of the entire kidney would certainly be a desirable method for the detection of intrinsic or extrinsic pathology of this organ. The possibility is suggested, therefore, of the future use of this method in the human being, for instance, in the case of one-sided surgical kidney disease. The pathologic kidney would store bismuth, and therefore concretions, cysts, tumors, etc., would stand out on the x-ray film. The healthy kidney would not store bismuth and would not be damaged by the ordinary therapeutic doses of bismuth, which have been established as safe in a long experience in the treatment of syphilis. This problem is under investigation.

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UNILATERAL HYPERTROPHY OF THE MASSETER MUSCLE

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INASMUCH as the masseter muscle contributes importantly to the configuration of the face, a malformation or tumor of this structure results in an early and conspicuous deformity. Such a lesion may be easily mistaken for a mixed tumor of the parotid gland, a salivary retention cyst, or an adamantinoma.

The rarity of primary tumors of the masseter is revealed by my failure to collect more than 9 cases in a review of the literature. Dudon,[1] in a thesis on this subject, reported the occurrence of 2 cases of cystic sarcoma and 1 case in which a fibrochondroma was identified. King[2] described a case of severe trismus in which the resected muscle had been almost totally converted into fibrous tissue. Tatum's[3] case of recurring fibroma of the masseter was undoubtedly an instance of fibrosarcoma. A case of rhabdomyosarcoma was reported by Larue.[4] Pantaleoni[5] observed the occurrence of a primary angioma of the masseter in 1 case and he collected 2 similar cases from the literature.

Nonneoplastic affections of this muscle are of such frequency as to deserve mention. Dudon[1] described 2 cases of hydatid cyst of the masseter and, in addition, he mentioned the involvement of this muscle in tuberculosis, trichinosis, actinomycosis, and myositis ossificans. Margarot, Rimbaud, and Ravoire[6] presented 3 cases of gumma of the masseter, in all of which the tumefaction disappeared with antisyphilitic therapy. An interesting case of a cyst situated in the right masseter muscle was reported by Beco.[7] He identified several small ranulas in the adjacent tissue, and consequently he concluded that it was a retention cyst of an accessory portion of the parotid gland. Duroux[8] described a case of asymptomatic bilateral hypertrophy of the masseter, the nature of which was undetermined.

CASE REPORT

W. K., white male, aged 19 years, was seen in consultation with Thomas Monks, D.D.S., on March 5, 1941, because of a tumor of the right jaw. In 1936 members of the patient's family observed an enlargement of the right side of his face. Earlier photographs reveal no facial asymmetry. During the past year the swelling reached sufficient size to become a source of embarrassment to the patient, and he had complained of mild discomfort in the region of the tumor. Except for a rather unusual fatigue associated with prolonged chewing, mastication was not interfered with. Not infrequently the buccal mucous membrane on the right side was traumatized during mastication. No facial tic existed. Dental examination revealed the presence of four impacted wisdom teeth.

Received for publication, Oct. 20, 1941.

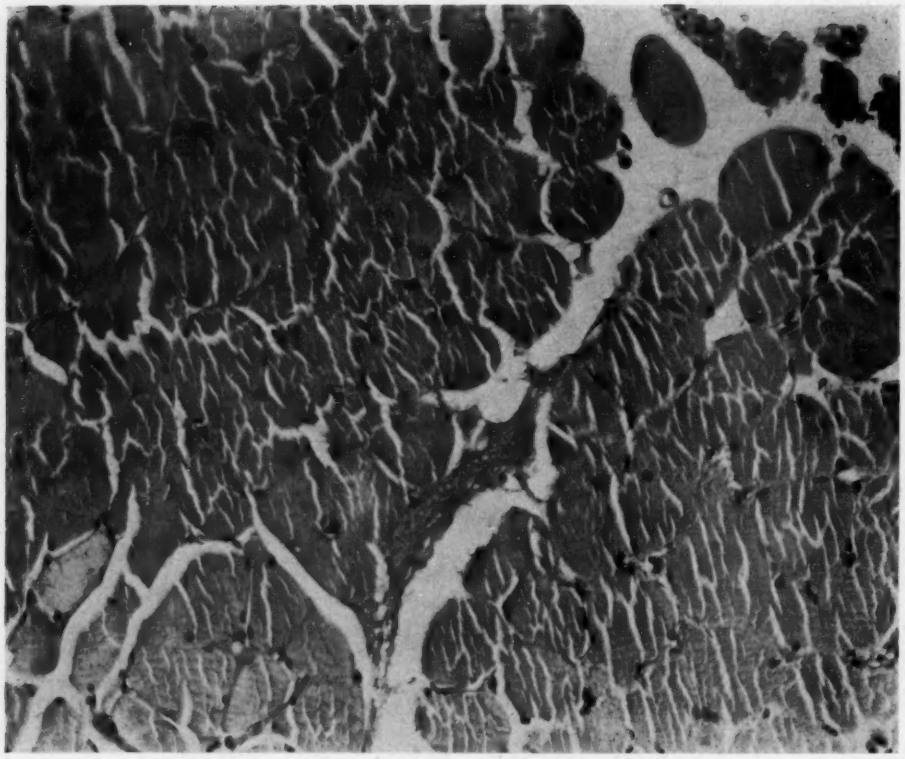
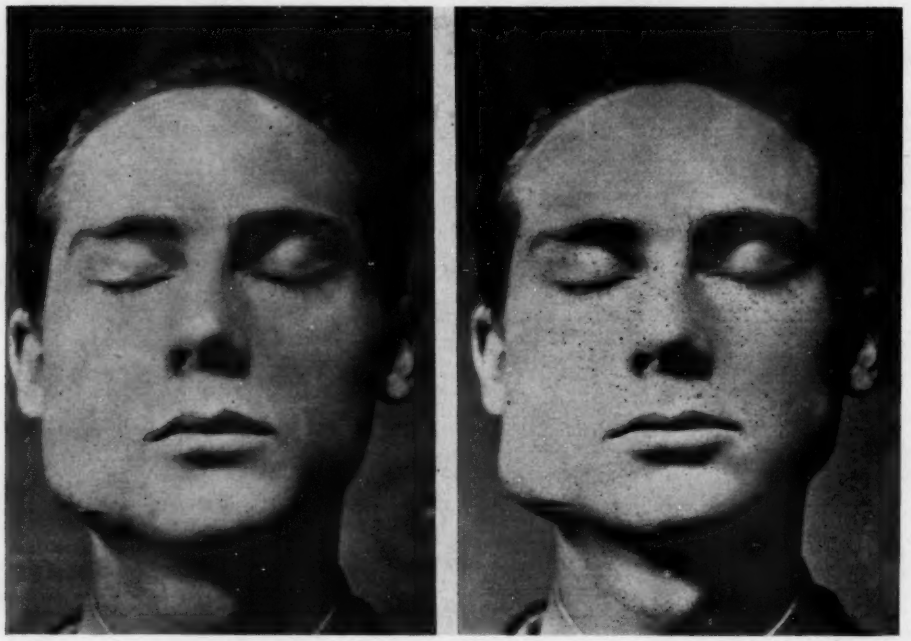


Fig. 1.—Photomicrograph of section of muscle biopsy showing hypertrophy of the individual fibers; no evidence of inflammation is present. (×515.)



A. *B.*

Fig. 2.—Photographs showing the size of the mass (*A*) with jaws relaxed, and (*B*) with jaws contracted.

On examination a soft, noncystic, and slightly tender mass, measuring 3 by 4 cm., was both visible and palpable immediately above and medial to the angle of the jaw on the right side. No palpable enlargement of the right parotid gland was found. Simultaneous palpation from within the oral cavity and on the surface revealed that the major portion of this mass presented externally. Saliva flowed freely from the parotid duct on the involved side. A roentgenogram of the right mandible showed no evidence of disease of the bone. The Kahn test was negative. A tentative diagnosis of tumor or retention cyst of the facial process of the parotid gland was made.

On March 13, 1941, under intratracheal nitrous oxide anesthesia, a 4 cm. incision was made along the superior border of the mandible. On exposure of the masseteric fascia, the underlying mass resembled thyroid tissue as seen through its intact capsule. The fascia was incised, and longitudinally disposed muscle fibers were encountered. Assuming that these fibers were overlying the tumor, the dissection was carried deeper into the muscle until finally the buccal mucosa was reached. It was

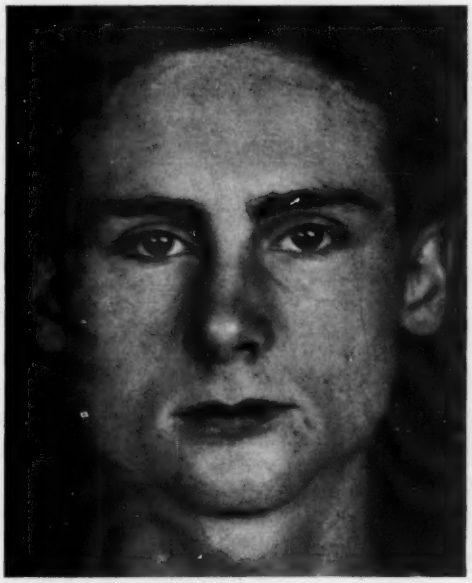


Fig. 3.—Photograph taken five months postoperatively showing diminution in the size of the hypertrophied masseter muscle.

then apparent that the mass consisted of a greatly hypertrophied masseter muscle. A biopsy of this tissue was submitted for pathologic examination to Dr. Vincent Dardinski who reported: "The tissue is composed of striated muscle, the individual fibers of which are thicker than normal; whether this can be construed as being a pathologic process is difficult to say because of the absence of any other pathologic changes [Fig. 1]."

One month after primary healing of the incision, it was noted that contraction of the jaws caused a conspicuous protrusion of the mass, probably as a result of herniation of the muscle fibers through the sutured masseteric fascia (Fig. 2). A slight but not unusual, prominence of the corresponding muscle on the opposite side was observed. Although the dental surgeon was of the opinion that the impacted wisdom teeth were in no way related to the muscle hypertrophy, these teeth were subsequently extracted. The patient was advised to avoid unnecessary use of the masseters, as in gum chewing, and to confine his mastication to the uninvolved side

as much as possible. Definite diminution in the size of the hypertrophied masseter is evident in a photograph taken five months postoperatively (Fig. 3).

COMMENT

The occurrence of this heretofore unreported condition of unilateral hypertrophy of the masseter muscle presents several problems. The cause of the hypertrophy in this case was undetermined. No dental or orthopedic basis for a compensatory hypertrophy was discovered. Evidence of an inflammatory myopathy was lacking in the histologic sections of the muscle biopsy. No evidence of syphilitic or tuberculous involvement of the muscle existed. The clinical diagnosis of this rarity, in retrospect, could have been made by combined intraoral and external palpation of the contracted muscle. Conservative treatment is recommended. Habit tics, gum chewing, and such actions that unnecessarily exercise the involved muscle should be avoided. Surgical resection of the muscle, in whole or in part, would probably only aggravate the facial deformity and, in addition, would expose the patient to the risk of suffering an injury to the facial nerve and the parotid duct. X-ray therapy of the involved muscle is mentioned only to condemn it.

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Editorial

The Use of Refrigeration Combined With Vasodilatation to Preserve Vitality in a Relatively Ischemic Extremity

THE WORK of Allen and his associates on the use of refrigeration as a preliminary to amputation in older individuals with primary degenerative arterial disease in which gangrene is imminent has done much to lower the mortality rate in these poor-risk patients. They have shown that in older patients with impending arteriosclerotic gangrene, with or without diabetes, the application of a tourniquet to the extremity rendering it totally ischemic combined with refrigeration of the extremity will not only retard bacterial invasion in such an extremity, but will permit amputation to be done safely without the use of any further anesthesia. Nothing is more dramatic than to see the ease with which an amputation can be done in such a poor-risk patient without anesthesia and to observe the uneventful convalescence which he has postoperatively.

Whereas these contributions of Allen and his associates in elderly patients with primary arterial disease of an extremity are of inestimable value, it is our opinion that refrigeration is probably of greater value in younger individuals whose vascular system is otherwise normal, but in whom there is an interference with the blood supply as a result of trauma. In these instances, refrigeration should be used not as a preliminary to amputation but in an attempt to decrease the metabolism of the part sufficiently so that the impoverished blood supply is capable of maintaining the viability of the extremity. Previously, in the presence of interference with vascularity of the extremities it has been the popular practice to apply heat; and yet according to the investigations of Allen, Freeman, Brooks, and Duncan, the use of heat in this way is probably the worst thing that can be done. As has been demonstrated by Brooks and Duncan, the production of a total ischemia in a rat's tail results in massive necrosis occurring within four hours if the tail is maintained at a temperature of 40° C. On the other hand, a similar degree of ischemia does not result in serious damage to anemic tissues for as long as four days if the temperature is maintained at 4° C.

Whereas it is extremely desirable, by decreasing the environmental temperature, to decrease the metabolism of the cells of the part to a sufficient degree that vitality can be maintained with an otherwise inadequate blood supply, it is equally undesirable to decrease further the blood supply of the extremity as a result of vasoconstriction produced by the application of cold. Therefore, it is obvious in those cases in

as much as possible. Definite diminution in the size of the hypertrophied masseter is evident in a photograph taken five months postoperatively (Fig. 3).

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The Use of Refrigeration Combined With Vasodilatation to Preserve Vitality in a Relatively Ischemic Extremity

THE WORK of Allen and his associates on the use of refrigeration as a preliminary to amputation in older individuals with primary degenerative arterial disease in which gangrene is imminent has done much to lower the mortality rate in these poor-risk patients. They have shown that in older patients with impending arteriosclerotic gangrene, with or without diabetes, the application of a tourniquet to the extremity rendering it totally ischemic combined with refrigeration of the extremity will not only retard bacterial invasion in such an extremity, but will permit amputation to be done safely without the use of any further anesthesia. Nothing is more dramatic than to see the ease with which an amputation can be done in such a poor-risk patient without anesthesia and to observe the uneventful convalescence which he has postoperatively.

Whereas these contributions of Allen and his associates in elderly patients with primary arterial disease of an extremity are of inestimable value, it is our opinion that refrigeration is probably of greater value in younger individuals whose vascular system is otherwise normal, but in whom there is an interference with the blood supply as a result of trauma. In these instances, refrigeration should be used not as a preliminary to amputation but in an attempt to decrease the metabolism of the part sufficiently so that the impoverished blood supply is capable of maintaining the viability of the extremity. Previously, in the presence of interference with vascularity of the extremities it has been the popular practice to apply heat; and yet according to the investigations of Allen, Freeman, Brooks, and Duncan, the use of heat in this way is probably the worst thing that can be done. As has been demonstrated by Brooks and Duncan, the production of a total ischemia in a rat's tail results in massive necrosis occurring within four hours if the tail is maintained at a temperature of 40° C. On the other hand, a similar degree of ischemia does not result in serious damage to anemic tissues for as long as four days if the temperature is maintained at 4° C.

Whereas it is extremely desirable, by decreasing the environmental temperature, to decrease the metabolism of the cells of the part to a sufficient degree that vitality can be maintained with an otherwise inadequate blood supply, it is equally undesirable to decrease further the blood supply of the extremity as a result of vasoconstriction produced by the application of cold. Therefore, it is obvious in those cases in

which refrigeration is used to decrease the temperature of the part and thus decrease its metabolism in a relatively ischemic extremity, that vasoconstriction must be prevented. As has been repeatedly shown by many, vasoconstriction is best prevented by blocking the vasoconstrictor impulses which are carried over the sympathetic nervous system. This is probably accomplished best by repeated chemical sections of the sympathetic ganglia by means of novocain or by prolonged chemical section by means of novocain and alcohol.

The correct amount of refrigeration in the younger individuals in whom the maintenance of viability of the extremity is desired is more difficult to determine than that in the individual in whom refrigeration is used as a preliminary to amputation. In the latter instance, the extremity is rendered totally ischemic by means of a tourniquet, and the extremity is packed in ice. In the former instance, this degree of refrigeration is undesirable and detrimental. For that reason it is imperative that the temperature be carefully controlled. In order to prevent actual injury to the skin by too intimate contact of the refrigeration medium, it is desirable, if the cooling is accomplished by means of ice bags, that the extremity be wrapped in one or two layers of thin sheet wadding. It is preferable, however, that a refrigerating boot into which cooled air can be introduced be used. The degree of refrigeration which is necessary probably varies in different cases. Generally a Fahrenheit temperature of forty to fifty degrees is considered optimum. This can and should be maintained for long periods of time. It is important that when the refrigeration is discontinued it be done gradually, that is, that there be a gradual elevation in the temperature over a period of a number of days. In this way massive edema of the part can be obviated.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT SURGICAL PHYSIOLOGY OF THE PANCREAS*

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INTRODUCTION

IT IS only recently that a new impetus has been given to the re-examination of the physiology of the pancreas. As is true of all research, this stimulus has not resulted from any one factor, but from the gradual accumulation of knowledge opening new avenues of thought. The abstract knowledge finally succeeds in supplying the tools needed for the reinvestigation of a problem which formerly had been studied by the tools then at hand, but allowed to end at a certain point. It is amazing that the most important digestive organ in the body is the "dark continent" of the intestinal tract. The appearance of a pure chemical stimulant and a slight change in approach has resulted in new and successful means of studying pancreatic function. A functional test has also appeared. The most recent and still controversial phase of study is the evaluation of a new lipotropic hormone. With the accurate determination of blood enzymes, the diagnosis of pancreatitis has been simplified. The importance of this is well understood. In the near future the study of pancreatic function promises to make strides equal to that of the other organs of the body. Several reports of evaluations of the result of surgery in hyperinsulinism have been published. Pancreatic secretions continue to be studied in broad abstract aspects.

HYPERINSULINISM

Harris[1] in 1924, two years after the discovery of insulin, predicted a syndrome due to hyperfunction of the islands of Langerhans, analogous to hypo- and hyperthyroidism. Subsequently, he reported five clinical but obvious cases of hyperinsulinism. In 1927 Wilder and co-workers[2] reported the first proved case which was due to carcinoma of the islet tissue of the pancreas with metastases. Analysis of the metastatic tissue revealed a high insulin content. Symptoms began three hours and twenty minutes after lunch, with a blood sugar volume of 55 mg. per cent.

*Read before the Graduate Surgical Seminar, New York University College of Medicine, Dec. 11, 1941, Dr. Arthur M. Wright, Director.

One hour later it was 27 mg. per cent, the patient meanwhile becoming stuporous. Whipple and Frantz[3] in 1935 established the diagnostic triad of symptoms: (1) nervous or gastrointestinal symptoms appearing in a fasting state; (2) blood sugar readings of 50 mg. per cent or less; and (3) immediate relief by administration of glucose. The symptomatology is rendered more complex by the known interrelation of the pituitary, thyroid, adrenal, liver, and sympathetic nervous system in sugar metabolism.

The statistics of operative results are truly impressive. In Whipple's[4] collected series of 82 cases there was a mortality of 16 per cent, or thirteen patients. Sixty-two of the remaining sixty-nine were cured of their spontaneous hypoglycemia. These figures show further improvement when we consider that a second operation or autopsy report will often disclose a tumor in a portion of the pancreas which was not obvious previously. David[5] says, "this would strongly imply that it is exceedingly hazardous to assume with careful selection of patients with hypoglycemia that a tumor of the islet cells is not present." A blind subtotal resection of pancreatic tissue may afford relief in the indicated case by revealing a tumor well imbedded, by revealing hyperplasia of islet tissue, or by decreasing the amount of insulin-secreting cells. For this purpose it is estimated that from two-thirds to four-fifths must be removed, allowing 60 to 90 Gm. as the normal weight of the pancreas. In David's collected cases he reports on a series of patients in whom no tumor was found at operation, but a portion of the pancreas was resected instead. In twenty-two the tumor was revealed at pathologic examination. The results were successful as one would expect from the removal of the tumor. In another group of 18 cases having 8 to 28 Gm. removed where normal pancreatic tissue or hyperplasia was found, eight patients were unimproved and four died. However, in a third group of 17 cases strictly satisfying the criteria of the disease where 35 to 60 Gm. were removed, eleven patients were cured, one improved, four unimproved, and one died. These last figures are most impressive and seem to indicate a definite avenue for future progress. Proper surgical exploration requires competent examination of the anterior surface of the pancreas, including reflection of the descending portion of the duodenum to expose the head of the pancreas adequately, and, if necessary, incision of the gastrocolic ligament or transverse mesocolon.

Whipple and Bauman[6] report a definite tendency to a diabetic glucose tolerance curve in patients with hyperinsulinism due to pancreatic adenomas, both before and after removal. Conceivably, the hyperactive adenoma has depressed the function of the remaining islet tissue. They place more faith in fasting blood sugar figures. Conversely, in 3 cases where three-fourths of the pancreas was removed the same tendency was manifest, but apparently the enormous reserve corrected the tolerance within two years. In several cases, after operation with no pan-

creatic juice entering the intestine, normal fat absorption took place. This was due, in all probability, to gastric, intestinal, and biliary lipase, and bacterial activity in the intestine. Kennard[7] reported a papillary cystadeno-carcinoma of the pancreas which showed mild diabetes post-operatively for ten months, the total follow-up period. Burtness and co-workers[8] report a case of hyperinsulinism in which oral and intravenous dextrose and insulin tolerance curves were used with considerable aid in the diagnosis. Following removal of the adenoma, the same tests revealed a decreased tolerance to glucose. Thus it is seen that the surgery of hyperinsulinism is well advanced.

FATTY LIVER IN RELATION TO THE PANCREAS

The relationship between the pancreas and fatty liver has been known for several years. However, it is still incompletely understood. Fisher[9] in 1924 showed that insulin alone could not adequately maintain depancreatized dogs nor enable the animals to completely recover their well-being. They were unable to live for more than a short while. The most relative change seen at post-mortem was an associated marked fatty infiltration of the liver. Since then, it has been definitely shown and repeatedly confirmed that if raw pancreas was added to the diet, in addition to insulin, the animals could survive. Furthermore, they could live for long periods of time and these changes did not occur. Hershey[10] in 1930 showed that 10 Gm. of lecithin added to the daily diet would prevent the fatty infiltration of the liver. Best and Huntsman[11] subsequently identified the active ingredient as choline. Pancreatic extract contains in addition to the various enzymes, only a small amount of choline, which Dragstedt[12] showed was not sufficient to influence the liver. He has been the most active proponent in favor of lipocaic as a hormone. This substance is contained in an alcoholic extract of beef pancreas. Its effectiveness is not due to its choline content since liver or brain, which contain large amounts of choline, are not effective. The effective amount of choline is 2 Gm. per day, whereas 100 Gm. of raw pancreas, the effective dose, has only one-sixteenth the required amount of choline. Dragstedt holds the external pancreatic secretion to be important, but not the factor in the prevention of fatty liver. He found that, in depancreatized dogs on a balanced diet and sufficient insulin to control urinary sugar, fresh active pancreatic juice by mouth did not cause the disappearance of fatty infiltration of the liver and return of blood lipids to normal. After six to eight weeks, the requirements for insulin are reduced to two to three units daily; the sensitivity to insulin meanwhile increases greatly. The obvious explanation is decreased glycogen storage in the liver, which occurs concurrently. Progressive emaciation, weakness and enlargement of the liver occur. If lipocaic is given to the animal in this stage, the liver promptly decreases in size, and the architecture returns to normal.

Also, the animal is no longer sensitive to insulin and indeed requires a larger amount of insulin to balance urinary sugar.

McHenry and Gavin[13] studied fat metabolism and synthesis in relation to pancreatic and liver extracts. They found a marked increase in body and liver fat containing a large amount of cholesterol due to synthesis in rats on a fat-free diet when they fed a liver fraction containing pantothenic acid and factor W. The above could also be accomplished by a diet containing thiamine but low in choline. The fatty liver of the thiamine diet would easily be prevented by feeding choline. The type due to the liver fraction was prevented by feeding lipocaic but not by choline. It was thus obvious that in this experiment the lipocaic did not function by virtue of its choline content, but perhaps because of its protein content. Brewer's yeast was incompletely effective in preventing fatty liver of this type, while rice-polishings concentrate was completely effective. Admittedly, the fatty liver in the depancreatized animals is not definitely similar to that produced by the liver factor. Since rice polishings and yeast will prevent the fatty liver in these experiments, it is suggested that lipocaic is not specific enough to be called a hormone. Montgomery and collaborators[14] made an attempt to determine whether lack of the external secretion of the pancreas caused fatty disease of the liver, since both pancreatectomized dogs and pancreatic duct ligated dogs invariably developed fatty infiltration. In a group of sixteen dogs, eight were ligated, of which four were controls, and eight had pancreatectomy performed, of which three were controls. The treated group were first fed raw pancreas until their strength returned and then were fed pancreatic juice from animals with Elman-McCaughan fistulas. Twenty weeks later the control group had fatty livers in which the fatty acid content varied from 15.1 per cent to 20.5 per cent, whereas, the others showed 3.11 per cent to 7.0 per cent. Both ligated and pancreatectomized groups were essentially the same. From these experiments one would conclude that it is the external pancreatic secretion which maintains normal lipid level of the liver. However, there is still the possibility that the final effective product is the result of the interreaction of pancreatic secretion and intestinal mucosa. The authors feel that it is not a pancreatic hormone. Entenman and coworkers[15] found that the cholesterol, phospholipid, and total fatty acid of the blood can be raised from its low level and be maintained at a normal figure in duct-ligated and pancreatectomized dogs by the daily ingestion of pancreatic juice. However, Entenman and Chaikoff[16] have shown that 36 mg. of choline per kilogram per day are sufficient to prevent the deposition of abnormal amounts of lipids in the livers of depancreatized dogs maintained on insulin even up to five months. In their studies with the feedings of raw pancreas, 250 Gm. contain 575 mg. of choline and it may be that chemical which exerts the curative or preventative effect. They have a pancreas fraction of one gram, derived

from five and five-tenths grams of raw pancreas which will accomplish the same when given by mouth daily and has only 100 mg. of choline. Obviously, in this fraction, it is not the choline which is curative. Kauer and Glenn[17] studied ten dogs with 17 per cent to 84 per cent of their pancreas removed. One animal with 66 per cent removed had a fatty liver transiently. Another with 71 per cent removed showed this definitely. One with 84 per cent removed did not show the usual fatty degeneration, but it developed diabetes. In congenital pancreatic steatorrhea or fibrosis and atrophy of the pancreas, the only tissue affected is the acinar tissue, and not the islets, yet fatty liver is a prominent feature. Cole and Howe[18] report a case with a severe degree of focal necrosis, atrophy, and fibrosis of the pancreas involving three-fourths of the pancreas with normal islet tissue and fatty infiltration of the liver. Their opinion was that lipocaic was effective, but had not established itself since vitamins and lecithin were equally effective.

The Council on Pharmacy and Chemistry of the American Medical Association,[19] in consideration of lipocaic, suggests that further investigation will be required to identify the active substance. Also, its use is considered highly experimental. Finally, since the frequent association of varying degrees of pancreatitis with gall bladder disease is now well-recognized, it may be deemed increasingly important to protect the liver with lipocaic or pancreatic juice.

SECRETIN

A study of the external pancreatic function of the pancreas has in the past been prevented by seemingly insurmountable obstacles. The secretion was inaccessible, a standard stimulus was lacking, and the juice finally obtained was invariably grossly contaminated with food, gastric contents, and the chemical stimulants used. With the introduction of secretin by Hammarsten and co-workers,[20] a potent pancreatic stimulus, without histamine or allergens, was made available. Diamond and his group[21] have continued the work in this country. The results have been so definitive that the secretin test may now rank to be as informative as the gastric test meal. A double gastroduodenal tube is used to collect the pancreatic juice and remove gastric secretions. This last is important in preventing the normal physiologic secretin mechanism from operating while the test is being performed. The recent work in this subject has been reported by Diamond and Siegel[22] who have studied pancreatic volume, bicarbonate, amylase, trypsin, lipase, and blood amylase and lipase. With experience, there are no difficulties to the method. Fully one-half of the tests performed have been done in the office. Essentially, a double tube is passed so that one portion remains in the stomach and another remains in the duodenum. Gastric and duodenal contents are removed with a suction of 50 mm. of water until a basal flow is established for twenty to twenty-five minutes. Secre-

tin is then injected intravenously in dosage of 0.75 mg. per kilogram of body weight. Specimens are collected at intervals for sixty minutes. Immediately following the injection, a sharp increase in the flow of pancreatice juice is obvious, reaching a maximum in ten minutes and gradually declining to the basal level in sixty to eighty minutes. The total output of volume, bicarbonate, and enzymes is tremendously increased though, due to dilution, the concentration of the enzymes falls. It has been established that many cases of chronic cholecystitis have chronic pancreatitis. Of seventeen patients studied, those with complications had abnormal tests. Acute pancreatitis gave grossly abnormal results comparable with the degree of involvement. In addition, the degree of recovery could be followed. In obstructive jaundice the test was of special value. Carcinoma of the head of the pancreas gave very low figures. With atresia of the common duct, or carcinoma of the bile duct the amounts were from slightly diminished to normal. Also studied were cysts of the pancreas, cirrhosis of the liver, toxic hepatitis, acute yellow atrophy of the liver, steatorrhea, diabetes, and a miscellaneous group. The tests revealed many instances of unsuspected pancreatic disease and showed decreased pancreatic function in many diseases which, heretofore, were not thought to affect the pancreas.

PANCREATIC SECRETIONS

Tucker and Ball[23] attempted to determine the role of carbonic anhydrase in bicarbonate secretion by the pancreas. If this enzyme catalyzes the change from carbon dioxide to bicarbonate, its destruction should markedly influence the rate of alkali formation. Accordingly, sulfanilamide and thiocyanate were administered while the pancreas was under maximum stimulation and output following secretin. Results indicate that sulfanilamide did not inhibit pancreatic flow or bicarbonate concentration, though the concentration in the cells was in the usual ratio between that of the blood and pancreatic juice. To explain contradictory reports, it was found that extracted carbonic anhydrase was inhibited by sulfanilamide when the enzyme was prepared from pancreas or other tissues. However, in the cells, sulfanilamide was without influence on the pancreatic secretion. As the output of bicarbonate by the gland was larger than could be explained, at least part of the bicarbonate must arise from cell metabolism. Thiocyanate gave similar results until toxic doses were given. Ball and collaborators[24] injected intravenously bicarbonate made from radioactive carbon. The radioactive bicarbonate was increased in the juice four to five times that of the serum. Since radioactive sodium is approximately the same concentration in the pancreatic secretion as in the plasma and the total carbon dioxide has the same ratio as the radioactive bicarbonate, the authors conclude the metabolic carbon dioxide is not the source of bicarbonate. Analyses of total carbon dioxide of pan-

creatic tissue give values below that of serum. The concentration of bicarbonate ions occurs in the cells and is derived from plasma. Hug,[25] in studying secretion of sulfanilamide by the pancreas after secretin or pilocarpine, found it to vary between 73 to 77 per cent of the blood concentration. Thomas and Crider[26] studied the secretagogue effect of products of protein digestion on the pancreas. They found the peptones powerful stimuli of certain functions of the gland. While the volume was increased, it was inferior to the action of hydrochloric acid. The active secretagogue was not identified, but the purified proteoses and some amino acids were effective. Since the result was a different secretion than that from secretin, it is suggested that the mechanism is nervous and similar to "vagus juice," "pilocarpine juice," "psychic secretion" and that following mecholyl. Comfort and Osterberg[27] studied a series of pancreatic stimulants with the purpose of determining the most practical for studying the pancreatic juice. Vitamin A and starch did not produce any apparent effect. Mecholyl was as potent but a more uniform stimulant than casein, fat, or prostigmine. Secretin was the choice stimulant for the study of fluid and bicarbonate output, and gave as satisfactory information as the others about the enzymes. Secretin and mecholyl gave the maximum "all out" stimulation since the hormonal and nervous mechanism was utilized. This latter combination appeared the most satisfactory to study the maximum output of the gland. The injectable stimulants have obvious advantages over the foods as they avoid contamination and are measured more accurately.

ACUTE PANCREATITIS

Claude Bernard[28] in 1855 was able to produce typical acute pancreatitis with the injection of bile and olive oil into the pancreatic duct. Opie[29] in 1903 demonstrated the relation between an impacted stone in the ampulla of Vater and acute pancreatitis. His was the first successful attempt to cause this disease by lodging a stone in the ampulla so that the biliary system and pancreatic ducts were converted into a continuous channel. From that time, it has been conventional to regard as the "modus operandi" the activation of trypsinogen in the pancreatic ducts by bile. Following this train of thought, the now active enzymes proceed to digest the pancreatic cells and supporting network with the liberation of additional trypsin. Eventually, blood channels are opened with hemorrhage and infarction. As a result the gland is torn and additional acini are opened with the liberation of further enzymes continuing the cycle. Cameron and Noble[30] did much to settle the anatomic basis for the reflux of bile by impacting a stone in the ampulla and injecting a colored dye. In 74 per cent they found a continuous channel. Reflux of bile may not only occur due to the impassable stone, but it is now generally felt that dyskinesia of the ampulla or local edema of the duodenum may be a prominent factor. Simple variations in the pressure

of the common pancreatic duct may allow the ready mixing of bile, pancreatic juice, and duodenal contents in the pancreatic ducts. Archibald[31] is a strong proponent of the theory that spasm may cause reflux into the pancreatic duct. He had observed the ampulla to close immediately upon the application of acid or gauze. He also found that increased pressure in the gall bladder, caused by bile or saline solution, would close the ampulla with regurgitation into the pancreas. Indeed, the reverse is also true since Diamond and Siegel, and Colp and Doubilet[32] have found active pancreatic enzymes in the bile from common duct drainage. To prevent the spasm from operating, Archibald now cuts the sphincter through the duodenum. However, it would seem that the sphincterotome as used by Colp and Doubilet[33] might simplify this. Archibald, unable to demonstrate digestion of the pancreas by trypsin or trypsinogen in vivo or in vitro, objects to the bile-activated trypsinogen theory of acute pancreatitis. By injecting infected bile into the pancreatic duct in small quantities under very low pressure, he was able to produce intense edema of the pancreas with subsequent necrosis. Pancreatic tissue placed in bile showed the most rapid autolysis and digestion. Colp and Doubilet[34] have shown that infected bile has a greater content of bile salts and Flexner[35] has demonstrated that it is the bile salts which cause the most rapid necrosis of normal pancreas.

Smyth[36] has revealed the importance of the vascular factors. After injecting droplets of mercury into the arteries of the pancreas, typical areas of acute hemorrhagic pancreatitis developed in each animal. However, these were focal or multiple focal with no resemblance to the spreading type. Rich and Duff[37] subscribe to the vascular basis of acute pancreatitis. In their monumental work, they demonstrated that activated trypsin could cause the varying degrees of pancreatitis depending upon the amount liberated. Lynch[38] reported 18 cases of pancreatitis. Of these, 3 were due to vascular occlusion with massive necrosis and hemorrhage. Seven cases of diffuse and focal pancreatitis did not clearly demonstrate the clinical cause, but definitely suggested small vessel occlusion, duct obstruction, or local infection. The 8 that remained were obviously due to obstruction somewhere in the pancreas, though the exact site could be demonstrated in only 4. Lynch attributed the condition to duct-cell metaplasia with obstruction due to the heaping up of the epithelial cells. Many fine photomicrographs illustrate these nodules growing into the ducts.

The lymphangitis theory as expounded by Deaver and Sweet[39] is no longer supported though it gave a very facile explanation. A lymphatic route from the common duct to the head of the pancreas has not been demonstrated.

Popper and Necheles[40] found that the lymph, portal, and peripheral blood had the same amount of amylase and lipase in fasting dogs. Following the injection of 100 to 200 cat units of secretin there was a rise

in blood enzymes. When the pancreatic duct was tied and bile was injected distally, the rise in blood amylase was obvious in five to ten minutes. This was seen mainly in portal blood and to a lesser degree in the lymph of the thoracic duct. Edmonson and Fields[41] reported a patient with acute pancreatitis who showed shock and tetany. Since the carbon dioxide combining power was forty-seven volumes per cent it was not due to acidosis. Reasoning that with fat necrosis neutral fat is split into fatty acids and glycerol, calcium could be removed to form soaps with fatty acids. Studies showed that the blood calcium may fall between the third and eleventh day. As much as 1,732 mg. of calcium may be present in two kilograms of the pancreas and adjacent fatty tissue. Lewison[42] found an incidence of pancreatitis of one in one thousand. In a study of blood amylase figures of 35 cases, he felt strongly that the blood enzymes were diagnostic. The rise in blood amylase must be sought for early as the elevation is only transient and disappears in a week. Rhodes[43] believes the blood amylase figures are of the greatest values early in the disease, but fluctuate widely and should be frequently repeated. He has made the observation and I have always believed that subsequent readings may be subnormal as the gland is increasingly destroyed. He also reserves surgery for those cases with supervening suppuration and not the acute, mildly, or severely ill patients. However, his specific reason is that a cholecystectomy does not drain the pancreas, except where a common channel exists, and this supposedly in a small number of cases. Popper and Plotke[44] studied blood amylase and lipase following intravenous injections of commercial trypsin containing large amounts of amylase and lipase. They also replaced 60 per cent of a dog's blood with that of another animal suffering from experimental acute pancreatitis. In another group, acetyl-β methylcholine and eserine were injected and the blood enzymes estimated. The results were applied to acute pancreatitis in man. In a relatively slightly damaged pancreas the blood enzymes are eliminated rapidly. A high level over several days indicates a continued replacement of blood amylase and lipase and a severely active pathologic process.

Ephedrine and atropine should be used as medical treatment to stimulate the sympathetic nervous system and decrease the vagal secretion of the pancreas. A stomach tube will remove the normal physiologic stimulus. Kaufman and Calhoun[45] advise early surgery routinely. Of 41 cases, 28 were subjected to surgery with a 42 per cent mortality. Thirteen were given medical treatment, with a mortality of 38.4 per cent. Although the results of surgery were inferior, they feel it is definitely better as more seriously ill patients were operated upon. Cholecystostomy with later removal and drainage down to the pancreas is performed. If biliary tract pathology is found, a decompression is allowed. Directly opposed to this, Nordmann's[46] mortality dropped from 50 per cent to 24 per cent under conservative therapy. Mikkelsen[47]

reported a 7.5 per cent mortality in 39 cases treated expectantly, although 50 per cent were acutely ill. However, cholecystostomy is still popular. I believe that it is most important not to remove the gall bladder as this may be urgently needed for anastomosis later.

Walters and Cleveland[48] find the only useful tests of pancreatic function are blood enzymes, lipase, and amylase, study of pancreatic ferments with or without secretin, and studies of the urine and stools.

ACUTE PANCREATITIS AND DIABETES

We are most prone to consider only the external secretory function of the pancreas in acute pancreatitis. While most of the pathology is localized in the ducts and acini of the pancreas, the islet cells are often more than temporarily damaged. Many mild diabetics are made worse and often this disease owes its inception to inflammation of the pancreas. Shumacher[49] in a series of 18 cases reported 27 per cent showing glycosuria during acute pancreatitis. A mild diabetic who suddenly, with little cause, developed a severe, intractable diabetic coma was found to have pancreatitis at autopsy. Lynch cites post-mortem results of a woman who had diabetes nine years previously with apparent recovery. Here was marked scarring of the pancreas, with obliteration of acini in some lobules, although ducts and islets were present in these areas. A patient whose case I had the opportunity to follow suffered a severe suppurative pancreatitis. The secretin test revealed the most marked diminution of pancreatic function I had seen. At no time was diabetes present during the year she was observed, though another mild attack of pancreatitis occurred.

CONCLUSIONS

1. A definite avenue for future progress has been indicated in surgery of the pancreas for hyperinsulinism.
2. The status of lipocaic as a hormone has been evaluated, indicating it is still in the experimental stage.
3. The secretin test has denfiite value in the study and diagnosis of pancreatic disease.
4. Acute pancreatitis should be treated conservatively. The etiology of this disease remains controversial.
5. Diabetes has a definite relationship to inflammation of the pancreas and may be initiated by acute pancreatitis.

Grateful acknowledgment is extended to Dr. Frank Co-Tui for his kind assistance.

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Review of Recent Meetings

REVIEW OF THE MEETING OF THE AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS, TENTH ANNUAL CONVENTION, ATLANTIC CITY, N. J., JANUARY 11-15, 1942

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THE TENTH Annual Convention of the American Academy of Orthopedic Surgeons was held in Atlantic City, N. J., January 11 to 15. During this meeting an innovation was made in the general program, a series of instructional courses being given in various subjects related to the field of orthopedic surgery. Advance registration was required for attendance at these courses. Many favorable comments were made regarding their general excellence.

The scientific program was initiated January 12. The following presentations were given.

Edwin Weinberg, Baltimore, Md.: **Two Cases of Late Rupture of the Extensor Pollicis Longus Tendon Following Colles' Fracture.**—A short review of the literature on this rare type of lesion was given. The rupture apparently occurs as a late complication. Its relationship to the original injury and the importance of early recognition and repair of the defect in the tendon were pointed out. Excellent results were obtained following delayed repair in the two cases presented.

O. A. Engh, Washington, D. C.: **The Steinman Pin in Fracture Fixation.**—The author presented a series of cases where Steinman pins were used widely to maintain position of the fracture fragments. The main emphasis was laid upon the insertion of the pins in an oblique direction, and then incorporation of the pins in plaster. By this means more rigid fixation at the fracture site was assured, and the possibility of rotation about the pins, or motion between the skin and the plaster edge minimized. A series of illustrative cases showing the results of the method as used by the author were presented. On the whole the results appeared satisfactory.

Lieutenant Commander Robert Mazet, Jr., U.S.N.: **A Report of Thirty Cases of Osteochondritis Desiccans.**—The various theories advanced to explain the etiology of this condition were discussed briefly. It was pointed out that even though trauma commonly caused the initiation of symptoms, it probably was not always the direct cause of the lesion. The majority of the cases shown were localized in the knee joint. The advantage of injection of air into the knee joint to localize a loose body more accurately was brought out in one case quite clearly. Uniformly good results were obtained in all cases following excision of the fragmented area of bone.

Randolph L. Anderson, Charleston, W. Va.: **The Clinical Use of the Chamberlain Technique in Back Examinations.**—The Chamberlain technique of x-ray examination in the study of low back pain is designed to discover the presence

Received for publication, Feb. 19, 1942.

of laxity in one or the other of the sacroiliac joints. It requires that three films be taken centering over the symphysis pubis: One with the patient standing with weight equally distributed on both feet; one with the patient standing on the right foot alone, and finally on the left foot alone. In the presence of laxity of a sacroiliac joint, there will be a slight rise of the pubic bone on the affected side. The author felt that in a series of 144 cases studied, the technique had been most helpful in discovering the presence of this lesion.

Austin Moore, Columbia, S. C.: **Vitallium Replacement of Upper Two-Thirds of Femur, Following Nailing for Non-Union of Neck of Femur, Subsequent Bone Graft for Giant Cell Tumor and Finally Resection of Bone.**—This presentation was given in the form of a motion picture film. Because of the aggressive nature of the tumor in the trochanteric region of the femur, the author felt it was necessary to resect the entire upper third of the femur including the head and neck. This area of bone resected was replaced with a vitallium mold which was then attached to the distal femoral fragment. The technical details of the operative procedure were shown. The end result which depicted the patient walking on the extremity was startling indeed. The author pointed out several defects in the procedure discovered during the course of observation and suggested improvements which might be used to advantage in other similar cases. The successful replacement of such a large defect in a weight-bearing bone, with a vitallium mold, will certainly open a further field of reconstructive surgery.

H. Alvin Jones, Baltimore, Md.: **Congenital Synostosis of the Cervical Spine (Klippel-Feil Syndrome)—A Study of Case Reports.**—The author summarized the findings in some 31 cases studied. The nature and theories as to the etiology of the defect in the vertebral column were summarized briefly. He felt that the deformity resulting from its presence could be minimized by early recognition, prolonged physical therapy, and adequate brace support. Photographs of several cases treated in accordance with this plan were shown.

Major Leonard Peterson, U.S.A.: **Two Cases of Interscapulothoracic Amputation.**—The technique of an interscapulo-thoracic amputation was reviewed. The author then presented the case histories of two patients so treated at Walter Reed Hospital in Washington, D. C. The first case was that of a Ewing tumor involving the upper third of the humeral shaft. Early metastatic lesions in the lungs were reported. The second case, a patient with a fibrosarcoma of the shoulder girdle, was apparently successful in arresting progress of the lesion to date. A prosthesis had been furnished to compensate for the cosmetic deformity of the shoulder. End result photographs showing the patient dressed gave a very satisfactory impression.

William Rogers, Boston, Mass.: **The Treatment of Fracture and Dislocation of the Cervical Spine.**—The author advocates a radical departure from the usual method of treating fracture dislocation of the cervical spine. He feels that the results from previous conservative traction and prolonged immobilization have not always been satisfactory in preventing recurrence of the dislocation once support has been removed. Furthermore the length of recumbency can be appreciably shortened without danger if his regime is followed exactly. The essential steps in the proposed method of treatment are as follows: (a) The use of a mechanical Thomas collar for protection until an accurate x-ray examination has been made and studied. (b) Skeletal traction, the first step in actual treatment, is applied as quickly as x-rays are taken, to safeguard the cord and roots against further injury, and to pave the way for complete reduction. The usual measures are taken to minimize complications during the next several days.

As soon as the patient's general condition will warrant (c) an open operation is done and the reduction completed. (d) Internal fixation of the dislocation is assured by the use of an autogenous bone graft secured with wire. (e) When wound healing is complete an ambulatory brace is fitted and worn. The author feels this method is quite as efficient as the older type of prolonged plaster fixation, particularly since the graft is firmly fixed in situ. A series of cases so treated were reviewed.

Rudolph S. Reich, Cleveland, Ohio: **Treatment of Flexion Deformities of the Knee.**—The author reviewed briefly the various causes leading to the development of a flexion deformity of the knee joint, and voiced a plea for more widespread dissemination of knowledge as to the necessity of preventing their occurrence. He emphasized the point that the majority of these deformities can be easily avoided if proper splinting is furnished the patient during the acute stages of their illness. When the contracture had become fixed and there was no contraindication to surgical correction, the author felt that his method of correction had proved valuable. He advised exposure of the posterior aspect of the thigh and popliteal space through two incisions, one over the biceps tendon laterally, and the second along the lateral edge of the semimembranosus tendon. Through the lateral incision the tendon of the biceps femoris muscle is isolated and a Z-type lengthening done. Through the medial incision the internal hamstrings are lengthened and a check made on the degree of extension obtained. If further correction is needed the origin of the gastrocnemius is stripped loose from the femur. As a final measure only, is posterior capsulotomy of the knee joint advocated. The author stressed the fact that with this type of exposure a better view of the posterior portion of the knee could be obtained, and a more rational attack made upon the various factors causing the contracture to persist.

Frederic C. Bost, and **Verne Inman**, San Francisco, Calif.: **Pathology of Recurrent Dislocation of the Shoulder: Report of Bankhart's Operative Procedure.**—In July, 1938, Bankhart reported the pathology of recurrent dislocation of the shoulder as proved by him in 27 consecutive cases. The lesion consisted of a tear of the glenoid labrum and the repair of the dislocation was effected by reattachment of the glenoid labrum.

The authors report verification of Bankhart's findings, based upon anatomic studies, and clinical observations in 10 cases operated upon for recurrent dislocation of the shoulder and repaired according to Bankhart's technique. They pointed out the fact that the presence of a defect in the glenoid labrum could be demonstrated in several of their cases by x-ray views taken in a tangential plane. The difficulty encountered in obtaining exposure of the glenoid labrum at the time of operation was pointed out as constituting one undesirable feature of this particular type of repair.

Toufick Nicola, Montclair, N. J., in his discussion of this paper described a series of experiments done by him on cadavers attempting to reproduce a dislocation of the humeral head. His conclusions were two: (a) If the humerus is merely abducted, then, as it impinges against the acromion and the force is continued, the capsule of the shoulder joint tears loose from the humerus or the neck of the scapula. (b) If, however, in addition to the abduction force, an impaction force is applied the capsule tears from the glenoid labrum. In four cases of acute dislocation of the shoulder explored at operation, these experimental findings were corroborated. He felt that any dislocation of the shoulder associated with a defect in the glenoid labrum would predispose toward a recurrent dislocation of the shoulder; that one associated with a tear of the capsule from the humerus or neck of the scapula would not do so. The author felt that

his own method of repairing a recurrent dislocation of the shoulder was equally satisfactory and technically a much easier operation than Bankhart's procedure.

William T. Green, and **Sidney Ferber,** Boston, Mass.: **Eosinophilic or Solitary Granuloma—Is It a New Disease?**—The authors presented their findings in a series of 12 cases followed over a period of years. The disease process was uniformly characterized by localized destructive lesions of bone which were either single or multiple. In the single lesions, the defect seen on x-ray was identical with that of solitary bone cyst. In the multiple lesions, the distribution and roentgen appearance resembled that of metastatic malignancy or myeloma. One case showed twenty-six areas of involvement of the skeleton. The disease in all cases was limited almost completely to a destructive lesion in the skeletal system with no reactionary bone formation.

Careful clinical observations and biopsies were made in all instances. The lesions seemed to conform to the picture recently described as a new disease, "solitary granuloma of bone." The authors presented as their opinion, that this process was actually a variation of the same basic disease represented by Schüller-Christian's or Letterer-Siewe's disease. A most interesting scientific exhibit was shown to substantiate their conclusions further.

Robert L. Carroll, Los Angeles, Calif.: **The Rate and Amount of Increase in Muscle Strength Following Infantile Paralysis.**—A study of early and late after-effects of infantile paralysis in 1500 cases was made under a grant from the National Foundation for Infantile Paralysis. In judging the degree of residual paralysis Dr. Lowman's scale of 0-9 was used throughout this study. By means of statistical analyses an effort was made to determine the general pattern of return in muscle strength. The conclusion reached was that the greatest increase was found in the first six months after onset of illness, the average degrees of improvement representing three points on the Lowman scale. During the period from six months to ten years after onset, approximately one point more increase in muscle strength was gained. Though most of these patients did receive prolonged physiotherapy, no conclusion was drawn by the author as to the efficacy of these measures in promoting more rapid or complete return of power in any case.

Mather Cleveland, and **David M. Bosworth,** New York, N. Y.: **A Study of Gross and Microscopic Lesions in Tuberculosis of the Spine.**—The authors showed an extremely interesting scientific exhibit in conjunction with this presentation. They had collected a series of proved cases of tuberculosis of the spine with pre-operative roentgenograms, gross specimens obtained at autopsy, and films taken of the gross specimens after removal from the body. Following careful study of this material they felt they could state definitely that tuberculosis of the spine always appeared in one of two fashions: (a) as a process of caseation and necrosis in the body of the vertebra itself, the result of local emboli of tubercle bacilli, or (b) as an area of sclerosis in the body due to interference with the blood supply to this area which interference in turn could be attributed to stripping of the soft tissues from its surface by a spreading abscess. Since there were no vessels entering the intervertebral disk they felt that it was impossible for an embolus to reach this point, hence the opinion that narrowing of the intervertebral space represented one of the early signs of tuberculosis of the spine was erroneous. When involvement of the disk appears the process is already widely established in the adjacent soft tissues and probably vertebral bodies also. The earliest signs of embolic phenomena in the bodies of the vertebrae were therefore due to the resultant caseation and local necrosis which when viewed on the roentgenogram appeared as areas of mottling. When the

disease process involved the soft tissues predominantly and the sole bone changes were due to stripping of the soft tissues from the body of the vertebra, then the resultant sclerosis would appear as a local area of increased density. If spread of the latter process was to be kept to a minimum, frequent aspiration of the abscess would be a very worthwhile procedure. They have proved it to be so in a group of active cases of spine tuberculosis followed at Seaview Hospital. The detection of these early bone changes by means of x-ray examination is most difficult, at times impossible. The authors feel, therefore, that when spine fusion is attempted a much wider area of fusion should be secured than has heretofore been considered adequate.

J. B. Weaver, Kansas City, Mo.: **Calcification and Ossification of Semi-Lunar Cartilages.** The author presented a brief review of the literature published on this subject to date, quoting 76 cases from the literature and adding two additional cases of his own. The typical changes occurring in the cartilage were segregated into two main types, primary and secondary. In the primary form, the lesions appeared as a generalized calcification in all the menisci. The patient is usually over 40 years of age. The etiology of this condition is not clear. Conservative therapy seems best suited. The secondary form involves a single meniscus only. The patient is usually under 40 years of age. A localized zone of calcification in a single meniscus occurs. This may or may not be completely apparent upon x-ray examination. The presence of the lesion leads to synovial changes, pain, swelling and loss of motion. Excision of the involved meniscus usually leads to a complete restoration of function. The etiology can frequently be attributed to trauma.

Wallace H. Cole, St. Paul, Minn.: **Further Report on the Kenny Treatment of Infantile Paralysis.** Fifty-one cases had been carefully studied up to Dec. 1, 1941. The author stated that in his opinion the results obtained had been most satisfactory, since he had noted these patients were much more comfortable during the acute stage of their illness, and that contractures and stiffness were universally prevented. The Kenny treatment is designed to combat three essential factors considered to be present in the involved musculature. These are in Sister Kenny's opinion: (a) incoordination of muscle action, which may be present within the muscle itself, or which may be the result of a secondary spread of impulses by reflex means from adjacent involved musculature, (b) disorientation in local muscle action manifested by the inability of the patient to produce a contraction even though the motor pathways to that muscle are unimpaired, and (c) muscle spasm which is considered the cause of local pain, fibrillary twitching, etc.

Active treatment is instituted as early as possible following onset of the disease. No splints are used. The feet are supported against a foot board in the "standing position," the arms allowed to lie free by the sides. Hot fomentations are applied over the involved musculature, leaving the joints exposed as much as possible. In the average case these hot moist packs are changed every two hours during a twelve-hour period, none being used during the night. In the more severe type of infection they are changed more frequently, even every fifteen minutes. Controlled passive motion is instituted early, through a range of motion which is not associated with pain. Incoordination and disorientation are combated from the start by personal supervision and education of the patient to acquire a mental attitude of cooperation in producing motion either passively or actively. This latter phase of the treatment is considered essential by Sister Kenny. Its proper conduct will require an accurate knowledge of individual muscle action and body mechanics, as well as a personality sufficiently developed to acquire the full confidence of, and cooperation from, the patient.

The clinical impressions of the author were corroborated by similar observations reported by **Alan Deforest Smith** of New York City, **Edward L. Compere** of Chicago, and **Walter Blount** of Milwaukee.

Philip Lewin, and **Louis Scheman**, Chicago, Ill.: **Experimental Osteomyelitis.** The authors presented a preliminary report on the experimental production of a lesion simulating human osteomyelitis. They have used a broth culture of *Staphylococcus aureus* originally obtained from a patient with hematogenous osteomyelitis and subsequently passed through many rabbits. In the early work rabbits were used exclusively as experimental animals. The technique which proved successful was as follows: The animals received an immunizing subcutaneous injection and then were allowed to incubate for one week. At the expiration of this period 0.3 c.c. of sodium morrhuate were injected into one of the tibial metaphyses, followed in one hour by 0.2 c.c. of 1:50 dilution of a twenty-four-hour broth culture of *Staph. aureus* into the same metaphysis. A lesion very closely simulating the disease as encountered in the human being was universally produced. Roentgenograms, cultures, and microscopic examinations were made to prove this point. In the later stages of the experimental work identical results were obtained on dogs. This contribution opens a wide field for further experimental work on osteomyelitis, both chronic and acute. For years attempts have been made to reproduce in animals lesions in bone resembling human osteomyelitis, always with questionable success. The authors presented their technique as a uniformly successful method for experimental production of this disease, and suggested a few of the wide problems it may open for further investigation.

Alan Deforest Smith, and **Lawson E. Miller**, New York, N. Y.: **The Value of Laminograph in the Treatment of Chronic Osteomyelitis.** A short series of cases of chronic osteomyelitis were discussed, the histories reviewed, and x-rays shown, in which accurate localization of the offending focus in the shaft was masked in the ordinary roentgenogram. By means of the laminograph, it is possible to locate and treat these areas with accuracy. A radiopaque substance was injected into the open sinuses to substantiate the findings further. This appears to be a valuable adjunct to the treatment of obscure cases of osteomyelitis, when the apparatus is available for use.

Lenox D. Baker, Durham, N. C.: **The Report of the Use of Sulfonamides in Traumatic and Infected Wounds.**—An effort was made by the author to evaluate the true efficacy of the sulfonamides when used locally and systemically to control infection in the extremities. The work was made possible through a series of case reports made by various members of the Academy throughout the country. In the present report three classifications were used: (1) Chronic osteomyelitis (Table I); (2) Old compound fractures with infection (Table II); and (3) Fresh compound fractures (Table III).

TABLE I

CHRONIC OSTEOMYELITIS

	TOTAL	HEALED	INFECTED
Surgery plus chemotherapy	74	54	20
Sulfanilamide	11	7	4
Primary closure	4	4	0
Open method	7	3	4
Sulfathiazole	63	47	16
Primary closure	41	36	5
Open method	22	11	11

The results from the use of the sulfonamides, particularly sulfathiazole, in chronic osteomyelitis, according to the method of Dickson and Diveley, seemed most encouraging.

TABLE II

OLD COMPOUND FRACTURE WITH INFECTION

	TOTAL	HEALED	INFECTED
Open reduction plus chemotherapy	47	30	17
Sulfanilamide	14	7	7
Primary closure	7	5	2
Open method	7	2	5
Sulfathiazole	33	23	10
Primary closure	20	17	3
Open method	13	6	7

In this group, particularly those cases treated according to the technique advocated by Dickson and Diveley, similar encouraging results were obtained.

TABLE III

FRESH COMPOUND FRACTURES

	TOTAL	HEALED	INFECTED
Open reduction plus chemotherapy	270	217	53
Sulfanilamide	242	192	50
Sulfathiazole	28	25	3
Primary closure	252	205	47
Open method	14	11	3
Drained	4	1	3
Internal fixation	126	90	36

In an analysis of this group the author felt that he could not attribute any great value to the use of the drug locally, except to state that it did not cause any increase in the percentage of infections in compound fractures. Proper surgical technique and wound hygiene still appeared to be the major factors in controlling the amount and degree of infection in compound fractures.

The report on the whole is interesting but still not conclusive. It should be carried further and a longer follow-up made on groups (1) and (2).

Stuart A. Thomson, Toronto, Can.: **Treatment of Club Feet with Dennis-Browne Splints.**—The method used by the author is really a modification of original method as outlined by Dennis-Browne. Small malleable foot splints are used and the baby's foot strapped snugly to these with adhesive tape. The cross-bar is adjusted first to correct the forefoot adduction, then the varus of the heel, and finally the equinus deformity in order. The whole correction is obtained gradually, the force used being the force exerted by the baby in kicking. Primary correction is obtained during the first several weeks, and correction maintained for six to seven months in the metal plate and adhesive strapping. Boot-splints are fitted at the expiration of this time, and worn till the walking age is reached. A night-splint is used for the first two to three years, though free walking in a corrective shoe is encouraged from the start. The method is obviously of value in the very young infant group only, and has no place in any other group. An interesting motion picture showing end results of cases so treated was displayed.

Harry E. Mock, Chicago, Ill.: **The Management of Associated Injuries in the Presence of Skull Fracture.**—This report is based upon a nation-wide survey of 3,106 cases of skull fracture collected from nineteen hospitals. A careful tabula-

tion of all associated injuries was kept. The importance of careful examination was emphasized, since many associated injuries may be more serious in nature than the cerebral damage. A plea was voiced to avoid too energetic methods of examination and treatment of associated injury, in order to avoid unnecessary increase in the degree of intracranial damage and consequent rise in the mortality rate. A very careful regime of observation and treatment of primary skull fracture was presented, which when followed in detail gave definitely superior results. This consisted of intelligent management of the skull fracture and brain injury first, with the simplest type of temporary treatment of the associated injury, followed by intelligent management of the latter when the patient's condition warranted. A detailed review of this vast amount of material cannot be given properly in synopsis form. A careful study of the original article when published is strongly advised.

Charles F. Thompson, Indianapolis, Ind.: **Fusion of the Metacarpal of the Thumb and Index Finger to Maintain Functional Position of the Thumb.**—After the method of Allen in Birmingham, England, in which a keystone block of tibial cortex is used to fuse the metacarpal of the thumb to that of the index finger, maintaining the fixed rotation of the thumb in opposition to the fingers, the function of the so-called "paddle hand" may be markedly improved. The author presented a series of cases in which satisfactory results had been obtained with this method. The procedure is reserved for those cases where tendon transplant is not considered possible, and to those which show satisfactory grasping power. The same technique has proved of definite value in certain types of spastic paralysis. The procedure admittedly has a limited field of usefulness, but when indicated seems a most satisfactory answer to a difficult problem.

John H. Kuhns, Boston, Mass.: **The Orthopedic Treatment of Hypertrophic Arthritis of the Hip.**—The nonoperative procedures used for treatment of hypertrophic arthritis of the hip were discussed. One hundred and eighty-three patients were reviewed, 86 men and 97 women, who had been discharged from the hospital a year or longer. In 114 patients both hips were involved and in 69 one hip only was involved. Nonoperative treatment consists chiefly in attempts to remove mechanical factors which tend to make the condition worse. Chief among these is the increased forward inclination which comes with faulty body mechanics and increases with flexion deformity at the hip joint. This brings weight thrust upon the posterior part of the acetabulum rather than upon the strong and superior portion. In addition, muscular pulls are changed and muscular atrophy develops. Strain, fatigue and instability are the natural sequelae.

Treatment is directed primarily to bring weight bearing as nearly as possible upon the strong superior portion of the acetabulum. In addition such factors as obesity, endocrine disturbances and hygienic errors are corrected, if possible. A special pelvic belt is frequently necessary when the patients first become ambulatory. With special treatment complete relief of symptoms and ability to continue with their regular activities was observed in 29.7 per cent of the patients and partial relief in 36.8 per cent of the patients. Nonoperative treatment was least effective in young individuals with unilateral involvement and severe deformations of the femoral head. In addition to these measures for those who showed no improvement, manipulation of the hip was undertaken in eight instances, with marked improvement in deformity and in motion in seven. This procedure was of value where there was not much deformation of the femoral head. Roentgen therapy is a helpful measure for the relief of pain. It produces no other effect so far as could be determined. Relief of pain was observed after the use of roentgen therapy in 16 of 21 patients.

Ralph K. Ghormley, and **M. B. Coventry,** Rochester, Minn.: **Surgical Treatment of Painful Hips in Adults.**—This review covered the cases of painful hips of adults that have been treated by surgery in the Mayo Clinic during the years 1938, 1939, and 1940. These included all types of painful hips, mostly, of course, hypertrophic arthritis.

Such procedures as arthroplasty with vitallium cup, arthrodesis, acetabuloplasty, and drilling operations were used for the most part. The results from these procedures were given. The arthrodesis, of course, was the most certain way of relieving pain; however, with the cup arthroplasty, which was performed in 13 cases, they were able to get improvement in motion in 11 of the cases and improvement from the standpoint of pain in 9 of the cases. In 9 of the 15 cases in which acetabuloplasty was carried out improvement was noted in regard to the relief of pain and amount of motion. With drilling, which was done in 8 cases, there was improvement from the standpoint of pain in 4 cases and from the standpoint of motion in 2 cases. Simultaneous review of the cases not treated by surgery in the same interval convinced the authors that surgical procedures do offer a considerable amount of relief to this group of patients.